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CAP MOR Addendum

NDA 21-158 Factive (gemifloxacin mesylate)
Addendum to MOR of Acute Bacterial Exacerbation of Chronic Bronchitis

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NDA 21-158 Factive (gemifloxacin mesylate)
Addendum to MOR of Acute Bacterial Exacerbation of Chronic Bronchitis

This review is an addendum to Dr. Brad Leissa's review of ABECB for NDA 21-158 of December 18, 2000. For additional information on the pivotal ABECB studies, the reader is referred to Dr. Leissa's review. At the time the review of the original NDA was completed, efficacy had been demonstrated for the indication of ABECB, but there were still outstanding safety questions for which additional data was needed. This review focuses primarily on the additional ABECB studies that have been performed since the original submission for NDA 21-158.

Introduction:

The applicant seeks approval of gemifloxacin 320 mg X 5 days for the indication acute bacterial exacerbation of chronic bronchitis (ABECB) due to *Hemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Hemophilus parainfluenzae,* and ——— Several factors distinguish the sponsor's proposed ABECB indication from the proposed CAP indication:

1. No claim for activity against resistant organisms is made for the indication ABECB.
2. The duration of treatment sought is for 5 days for which 5-day packaging unique to the indication, is proposed.
3. In addition to establishing non-inferiority in efficacy against the study comparators, the applicant provides data regarding other findings from the ABECB studies. These additional findings are based on an analysis of quality of life measures, pharmacoeconomics and microbiological eradication. Only one of these findings is proposed as a label claim of earlier eradication of *H. influenzae* in patients that receive gemifloxacin.

Background:

Therapeutic alternatives and drug utilization for ABECB

Several classes of antimicrobials are indicated for the oral treatment of ABECB, but only 3 agents are registered as 5-day treatments for this indication. Moxifloxacin and gatifloxacin are both approved as 5-day therapies for ABECB and as 7-day therapies for CAP, whereas cefdinir is approved as therapy for ABECB for 5-10 days and as a 10-14 day therapy for CAP (and therefore has overlapping durations of therapy for both indications).

Community antibiotic utilization data for ABECB presented by the applicant indicates that 35% of the annual prescriptions for ABECB would be written for patients under 40 years of age. This data was based on a three-year average of drug use for a broad array of antibiotics, from the study by Scott and Levin presented by the applicant in appendix A of the applicant's background package.

Regulatory precedence

The guidance document for clinical trials for the indication ABECB currently states that clinical efficacy in the intent to treat (ITT) analysis serves as co-primary with the per protocol (PP) clinical efficacy analysis, and that evaluable patients must be both clinically and microbiologically evaluable. The guidance document does not stipulate a margin to conclude non-inferiority.

A supplemental application for ——— received an action of not-approvable as 5-day therapy for ABECB whereas it had previously been granted approval as a 7-10 day therapy for ABECB and CAP in the original NDA. Information that was considered in the risk benefit analysis for grepafloxacin was the fact that comparable clinical efficacy could not be established in the patients with bacterial pathogens in the supportive studies, that efficacy favored longer durations of

therapy in patients with severe ABECB, and that QT prolongation was an unresolved issue that was still being investigated at the time of the action date for that submission. The non-approval of grepafloxacin was based on a) failure to demonstrate equivalent efficacy in the ITT analysis, b) the inferior efficacy in patients with bacterial pathogens (including greater recolonization with *S. pneumoniae* and c) low efficacy rates in patients with severe ABECB.

On February 19, 2002, an Anti-Infectives Advisory Committee meeting was held to discuss the proposed approach for selection of delta in non-inferiority clinical trials, including acute exacerbation of chronic bronchitis. The conclusion of the presentation on ABECB at that meeting was that the benefit of comparators over placebo could not be reliably estimated and that patients with more severe disease may benefit from antibiotics. Active controlled studies in patients with severe ABECB or placebo controlled studies in patients with mild to moderate ABECB were proposed to better define the attributable benefit provided by antimicrobial therapy. However, it was also noted that a defined set of severity criteria has not been validated.

Impact of Resistance

No antibacterial has been awarded an indication for infections due to penicillin resistant *S. pneumonia* (PRSP) in the context of ABECB infections. The epidemiology of clinically relevant PRSP infections indicates that otitis media and pneumonia are the prevalent infections with this pathogen. Nonetheless, the chronic, recurrent nature of ABECB, and the antimicrobial prescribing patterns for bronchitis in the community raise concern for the development of antimicrobial resistance in the colonizing bacteria in patients with ABECB.

Regulatory history of Gemifloxacin

In the original NDA submission for gemifloxacin, Dr. Brad Leissa concluded that efficacy was demonstrated for gemifloxacin in the treatment of ABECB at a dose of 320 mg p.o. q.d. x 5 days. This review of the resubmission covers the 6 ABECB studies submitted in the original NDA, as well as 5 new clinical studies submitted at the request of the Agency. In this resubmission, the sponsor reanalyzed key efficacy and safety data from these 11 studies excluding the data from investigators where data integrity issues were raised by DSI.

The safety and efficacy of gemifloxacin was also discussed at an Anti-Infective Drugs Advisory Committee meeting (March 4, 2003). The majority of the committee (15/18) concluded that the benefits of gemifloxacin outweighed the drug's known risks for the indication of ABECB, with 2 opposing votes and 1 abstension. Several members indicated that while the ABECB data in the gemifloxacin NDA fulfilled current standards of non-inferiority in ABECB, the treatment-attributable benefit for this indication, in general, has not been adequately defined absent placebo controlled trials. A minority suggested that the agency should hold this indication until the sponsor can provide more efficacy data, preferably from placebo controlled studies.

Clinical Review:

Review of Efficacy

The reader is referred to the ABECB section of the Agency's Background Document (appended to the end of this review) which contains additional pertinent analyses and discussion regarding the clinical efficacy of gemifloxacin in ABECB. This review summarizes the efficacy results from all studies performed in support of the new drug application for gemifloxacin in the treatment of patients with ABECB.

NDA 21-158 Factive (gemifloxacin mesylate)
Addendum to MOR of Acute Bacterial Exacerbation of Chronic Bronchitis

In support of the Applicant's ABECB indication, data from 11 clinical studies to demonstrate safety and efficacy for ABECB were submitted. Dr. Brad Leissa has previously reviewed six of these studies (studies 001, 008, 061, 068, 069, and 070) in detail in the original submission of the NDA. The remaining 5 studies (Study 212, 112, 105,139, and 207) were made available on the request of Dr. Ed Cox and accompany this resubmission of the NDA on the basis of that request.

Three of the 11 ABECB studies were pivotal. All of the three pivotal studies were randomized, double blind, double-dummy, parallel group studies, that compared the clinical and microbiological efficacy and safety of oral gemifloxacin with an approved antibacterial comparator. All studies utilized 5 days of gemifloxacin.

Two of the 11 ABECB studies were supportive. The two supportive trials, 069 and 207, compared the clinical and microbiological efficacy and safety of oral gemifloxacin with oral trovafloxacin (200mg QD for 5 days) and to parenteral ceftriaxone followed by oral cefuroxime, respectively. Of note, the comparator dose utilized in Study 069 was based on the European approved comparator dose and differed from the US FDA approved dose of 100 mg po QD for 7-10 days.

Three of the 6 remaining ancillary studies utilized the proposed 5-day duration of gemifloxacin therapy for ABECB (Study 112, Study 105, and Study 139). In these three studies, a total of 1205 patients received gemifloxacin for 5 days or clarithromycin comparator for 7 days. Study 112 was designed to evaluate the health economics impact of gemifloxacin 5-day therapy in ABECB. Study 105 evaluated the safety and efficacy of gemifloxacin given for 5 days in patients with severe ABECB. Study 139 was a health economics study developed to assess the comparative costs of gemifloxacin five-day therapy to that of clarithromycin 7-day therapy in ABECB.

The remaining 3 ancillary studies (001, 008 and 061) of gemifloxacin efficacy and safety in ABECB utilized either 7 or 10 day treatment durations. The applicant seeks approval only for the 5 day ABECB regimen. Hence, these studies are not reviewed here and are not represented in the Medical Officer's efficacy analysis. However, the safety of the 955 patients who received gemifloxacin in these studies is reviewed in aggregate with the other studies.

An aggregate of 2258 patients with ABECB received gemifloxacin 320 mg X 5 days in the comparative trials submitted in the NDA. The overall outcomes for these patients were similar to those patients that received the study comparators. The comparative efficacy in the principal and supportive studies is discussed below.

Table 1
Acute Exacerbation of Chronic Bronchitis: Completed Studies

Study	Gemifloxacin Regimen (N*)	Duration (days)	Comparator Treatment Regimen	Duration (days)	Study Sites	Demographics** M:F ratio Mean age (range in yrs)	Clinical Efficacy in Clinical Per Protocol Population at Follow-up	Deaths SAE AEs D/C for AE (gemi:comparator)
PIVOTAL STUDIES								
068 IIIa	320mg qd (N=340	5	clarithromycin 500mg bid (N=304	7	Europe, U.S., Canada	165/175 58.8 (36-88)	86% vs 85% (-4.7, 7.0)	2:1 9:13 169:190 8:14
070 IIIa	320mg qd (N=304)	5	Amoxicillin/ Clavulanate 500/125mg tid (N=396)	7	Europe	162/142 64.2 (40-92)	94% vs 93% (-3.9, 4.6)	3:0 10:5 95:104 10:9
212 IIIb	320mg qd (N=182)	5	levofloxacin 500mg qd (N=179)	7	Europe, U.S.	93/89 61.6 (34-90)	88% vs 85% (-4.7, 10.7) 78% vs 86% **(-23.8, 9.2)** @	0:1 5:12 72:60 4:10
Total	826					420/406 (49.2% female)		
SUPPORTIVE STUDIES								
069 IIIa	320mg qd (N=302)	5 days	trovafloxacin 200mg qd (N=314)	5	Europe	185/117 60.8 (28-91)	92% vs 98% (-9.2, 9.0) @	1:4 7:8 98:115 5:12
207 IIIb	320mg qd (N=138)	5 days	ceftriaxone 1g IV qd / cefuroxime 500mg bid (N=136)	1-3/ 7	Europe, Mexico, South Africa.	103/35 68.1 (42-90)	87% vs 81% (-3.9, 14.9)	2:2 9:11 64:50 4:6
Total	440					288/15 (34.5% female)		
Other Studies utilizing the 5 day gemifloxacin regimen								
105 severe (1999-2000 phase IIIb)	320mg qd (N=83)	5 days	clarithromycin 500mg bid (N=80)	7	Europe, U.S.	47/36 64.1 (40-81)	**62%** vs 68% no CI presented	1:0 3:3 23:25 5:2
112 IIIb	320mg qd (N=908)	5 days	clarithromycin 500mg bid (N=897)	7	Europe, Australia N. & S. America	444/459 67.2 (39-97)	43% vs 35% no CI presented	12:9 28:37 381:423 28:37
139 IIIa	320mg qd (N=214)	5 days	clarithromycin 500mg bid (N=224)	7	U.S., Canada	108/106 58.5 (37-88)	71% vs 59% (-2.5, 22.6)	See 068
Total	991					599/606 (50.3% female)		
Other Studies utilizing 7 and 10 day gemifloxacin regimens								
008 IIIa	320mg qd (N=293)	7 days	levofloxacin 500mg qd (N=293)	7	U.S., Canada	149/131 57.7 (34-85)	82% vs 86% **(-10.7, 2.8)** 76% vs 97% **(-35.3, 7.6)** @@	24:1 15:5 173:152 13:12
001 (phII)	320mg qd, (N=64) 160mg qd 80mg qd	10 days	ofloxacin 400mg bid	10	Europe, N.America		85%, 87% & 82% vs 91%	
061 IIIa	320 mg qd (N=261)	7 days	-	-	World-Wide except N. America	260/217 57.8 (18-88)	91%	4 24 221 20
Total	955							

* N=number of patients randomized to gemfiloxacin. Bolded studies included data pertaining to additional findings in ABECB.
** data pertains to gemifloxacin arm
@data pertains to Bacteriology PerProtocol at FollowUp
@@bacteriologic success in Bacteriologic PerProtocol at FollowUp

Clinical Efficacy of Gemifloxacin in the Principal Studies of ABECB

The three principal studies (Study 068, 070, 212) were randomized, double blind, double-dummy, parallel group studies, that compared the clinical and microbiological efficacy and safety of oral gemifloxacin 320mg once daily for 5 days with an approved comparator given for 7 days. The inclusion and exclusion criteria were consistent with the Draft Guidance on ABECB "Guidance for Industry: Acute Bacterial Exacerbation of Chronic Bronchitis — Developing Antimicrobial Drugs for Treatment

Clinical response, based on the resolution of signs and symptoms of ABECB in the Clinical Per Protocol Population (CPP) at follow-up (FU), served as the primary efficacy parameter in the principal clinical studies. Secondary endpoints included bacteriological and clinical responses in the patients with an identified pathogen (the Bacteriology intent to treat (BITT) and Bacteriology Per Protocol Population (BPP). None of the studies were designed to test non-inferiority for secondary endpoints.

The following table summarizes the key design elements for the principal studies in ABECB.

Table 2
Study Design of Principal ABECB Studies

	Study 068	Study 070	Study 212
DESIGN:	randomized, double-blind, double-dummy, multicenter, parallel group	Same as 068	Same as 068
Gemifloxacin regimen	320 mg qd x 5 days	Same as 068	Same as 068
Comparators	Clarithromycin 500 mg bid x 7 days	Amoxicillin/clavulanate 500/125 mg tid daily x 7 days	Levofloxacin 500 mg qd x 7 days
Countries	Europe, USA and Canada	Europe	Europe and USA
Primary Efficacy Analysis	Clinical response in the clinical per protocol population at follow-up (PP FU)	Same as 068	Same as 068
Protocol-specified non-inferiority limit	-10	-10	-13
Number of centers	93	112	62
Number of patients randomized to gemifloxacin	340	304	182

Demographic characteristics were equally balanced between treatment arms for all studies. The study population generally consisted of middle aged, white, long-term smokers, with a mean 12-year history of ABECB and 1-4 exacerbations of ABECB in the past year. Males and females were equally represented in the principal studies. About a third of patients in Studies 070 and 212 had a FEV1<50% of predicted. Patients with severe ABECB (stage 3) were a minority (~3%).

The three pivotal studies that enrolled over 600 gemifloxacin-treated patients find that gemifloxacin was non-inferior to the study comparators in the treatment of ABECB. The point estimates for the clinical efficacy of gemifloxacin ranged from 86.0% to 93.6%, with similar estimates for the three comparators clarithromycin, amoxycillin-clavulanate and levofloxacin. Of note the lower bounds of the 95% CI for these studies were within -5 percentage points of zero. The Agency concurs with this finding

of non-inferior clinical efficacy for gemifloxacin in patients with ABECB. Two other supportive studies and 5 other ancillary studies support this efficacy conclusion.

Table 3
Clinical and Bacteriological Response at Follow-up in the Principal ABECB Studies

	Success Rate		
	Gemifloxacin	*Comparator*	*Treatment Difference*
	% (n/N)	*% (n/N)*	*% (95% CI)*
Clinical Response in the CPP Population			
068	*86.0 (239/278)*	*84.8 (240/283)*	*1.2 (-4.7, 7.0)*
070	*93.6 (247/264)*	*93.2 (248/266)*	*0.3 (-3.9, 4.6)*
212	*88.2 (134/152)*	*85.1 (126/148)*	*3.0 (-4.7, 10.7)*
Clinical Response in the CITT Population			
068	*80.0 (272/340)*	*78.2 (272/348)*	*1.8 (-4.2, 7.9)*
070	*88.5 (269/304)*	*88.9 (263/296)*	*-0.4 (-5.4, 4.7)*
212	*85.2 (155/182)*	*78.1 (139/178)*	*7.1 (-0.9, 15.1)*
Bacteriological Response in the BPP Population			
068	*85.0 (34/40)*	*72.7 (32/44)*	*12.3 (-4.9, 29.5)*
070	*90.9 (40/44)*	*79.5 (35/44)*	*11.4 (-3.3, 26.0)*
212	*78.4 (29/37)*	*85.7 (42/49)*	*-7.3 (-23.8, 9.2)*
Bacteriological Response in the BITT Population			
068	*76.0 (38/50)*	*62.1 (36/58)*	*13.9 (-3.3, 31.3)*
070	*82.4 (42/51)*	*75.5 (37/49)*	*6.8 (-9.1, 22.8)*
212	*75.0 (33/44)*	*80.0 (48/60)*	*-5.0 (21.3,11.3)*

Bacteriological Efficacy of Gemifloxacin in the Principal Studies of ABECB

In two of the three pivotal studies, point estimates were slightly higher for gemifloxacin in the analysis of bacteriologic efficacy in both the per protocol and intent to treat analysis. However, in the pivotal Study 212, the point estimates were slightly higher for the comparator levofloxacin, although the difference was not significant given the small number of evaluable patients.

The per pathogen bacteriologic responses in the pivotal ABECB studies finds comparable efficacy rates between gemifloxacin and the comparators for all pathogens studied. Although less than 10 patients had ——— in the pivotal studies, a total of 34 of 38 patients with ——— related ABECB were successfully treated in all the ABECB studies submitted to the NDA.

The per pathogen bacteriologic outcomes in the bacteriological per protocol population are summarized in Table 3.

Table 3
*Per Pathogen Bacteriologic Eradication in the Pivotal ABECB Studies**

Pathogen	Gemifloxacin		Comparator	
Hemophilus influenzae	*n/N*	*%*	*n*	*%*
068	*11/12*	*91.7*	*6/6*	*100*
070	*14/14*	*100*	*14/15*	*93.3*
212	*7/7*	*100*	*10/11*	*90.9*
TOTAL	*32/33*	*97.0*	*30/32*	*93.7*
Streptococcus pneumoniae				
068	*6/7*	*85.7*	*5/5*	*100*
070	*6/6*	*100*	*8/8*	*100*
212	*4/4*	*100*	*4/5*	*80*
TOTAL	*16/17*	*94.1*	*17/18*	*94.4*
Moraxella catarrhalis				
068	*5/5*	*100*	*5/5*	*100*
070	*13/14*	*92.8*	*12/12*	*100*
212	*5/6*	*83.3*	*14/14*	*100*
TOTAL	*23/25*	*92.0*	*31/31*	*100*
Hemophilus parainfluenzae				
068	*6/6*	*100*	*5/5*	*100*
070	*2/2*	*100*	*0*	*0*
212	*7/7*	*100*	*5/6*	*83.3*
TOTAL	*15/15*	*100*	*10/11*	*90.9*

Clinical Efficacy of Gemifloxacin in the Supportive Studies of ABECB

Two clinical trials, Study 069 and 207, provided additional supportive evidence of the efficacy and safety of gemifloxacin 320 mg po qd for 5 days in the treatment of ABECB. Study 069 was of identical design as the principal studies, however, the dose of the comparator, trovafloxacin, utilized in Study 069 was based on the approved dose in Europe (200 mg qd for 5 days) whereas the approved dose in the United States is 100mg qd for 7-10 days. Hence, Study 069 was considered as a supportive rather than a principle study. The population of patients recruited into Study 069 was very similar to the patient populations in the principal clinical studies in ABECB in terms of baseline characteristics and severity of ABECB.

Study 207 was designed to investigate the safety and efficacy of gemifloxacin in hospitalized patients with ABECB and the impact of oral versus parenteral therapy on time to discharge and cost. Compared to the study population in the pivotal trials, patients in Study 207 were slightly older and had more frequent exacerbations of

Table 4
Selected Demographic and Baseline Characteristics in the Supportive ABECB Studies

	Study 068		Study 070		Study 212		Study 069		Study 207	
	Gemi N=340	Clari N=351	Gemi N=304	Amox/Clav N=296	Gemi N=182	Levo N=179	Gemi N=302	Trova N=314	Gemi N=138	Ceftr IV /Cefurox po N=136
Age										
Mean Age (SD)	58.8 (12.0)	58.6 (11.9)	64.2 (11.7)	63.9 (12.1)	61.6 (11.6)	63.4 (10.5)	60.8 (11.0)	62.4 (11.2)	68.1 (9.8)	67.1 (10.3)
Exacerbations (past 12 months)										
0	65 (19)	66 (18.8)	19 (6.3)	24 (8.1)	25 (13.7)	20 (11.2)	31 (10.3)	36 (11.5)	0	0
1-4	236 (69.4)	245 (69.8)	226 (74.3)	231 (78.0)	143	136 (76.0)	230 (76.2)	240 (76.4)	98 (71.0)	90 (66.2)
>4	36 (10.6)	40 (11.4)	58 (19.1)	41 (13.9)	14 (7.7)	23 (12.8)	38 (12.6)	37 (11.8)	40 (29.0)	46 (33.8)
Use of Supplemental Oxygen, n (%)										
Yes	32 (9.4)	23 (6.6)	14 (4.6)	9 (3.0)	18 (9.9)	19 (10.7)	8 (2.6)	12 (3.8)	34 (24.6)	33 (24.3)
Use of Systemic Steroids in last year, n (%)										
Yes	72 (21.2)	75 (21.4)	76 (25.0)	72 (24.3)	50 (27.5)	52 (29.2)	73 (24.2)	96 (30.6)	65 (47.1)	61 (44.9)
Current Smoker*, n(%)	*smoked regularly in last month		*smoked regularly in last month		*Currently smoke		*Smoked regularly in last month		*Current smoker	
Yes	146 (42.9)	161 (45.9)	130 (33.9)	117 (39.5)	81 (44.5)	67 (37.5)	114 (37.7)	117 (37.3)	27 (19.6)	30 (22.1)
Number of Pack Years patients has smoked n (%)										
0	72 (21.2)	80 (22.8)	96 (31.6)	96 (32.4)	38 (20.9)	39 (21.9)	99 (32.8)	83 (26.4)	28 (20.3)	30 (22.1)
>0-30	123 (36.2)	123 (35.0)	112 (36.8)	113 (38.2)	62 (34.1)	43 (24.2)	120 (39.7)	142 (45.2)	61 (44.2)	58 (42.6)
>30	143 (42.1)	147 (41.9)	92 (30.3)	82 (27.7)	82 (45.1)	96 (53.9)	83 (27.5)	89 (28.3)	49 (35.5)	48 (35.3)

ABECB in the last 12 months. Many required oxygen and were treated with systemic corticosteroids, indicators that the patients may have been considered to have more severe ABECB. However, these indicators have not been shown to correlate with the need for parenteral antimicrobial therapy. This study was not blinded (open-label) and patients in Study 207 were recruited from centers in Europe, Mexico and South Africa, and did not include patients in the United States.

In Study 069 the response rate in the CPP at follow-up was 91.5% for gemifloxacin and 87.6% for comparator. The clinical response rate in the CPP at follow-up in Study 069 was similar to those observed in the principal clinical studies. In Study 207 the clinical response rate in the CPP at follow-up was 86.8% for gemifloxacin and 81.3% in comparator. The response rates in Study 207, which enrolled hospitalized patients were lower than the success rates observed for the principal studies.

Table 5
Clinical and Bacteriological Response at Follow-Up in the Supportive ABECB Studies

	Success Rate		
	Gemifloxacin	*Comparator*	*Treatment Difference*
	% (n/N)	*% (n/N)*	*% (95% CI)*
Clinical Response in the C PP Population			
069	*91.5 (249/272)*	*87.6 (241/275*	*3.9 (-1.2,9.0)*
207	*86.8 (105/121)*	*81.3 (91/112)*	*5.5 (-3.9,14.9)*
Clinical Response in the Clinical ITT Population			
069	*89.4 (270/302)*	*83.1 (261/314)*	*6.3 (0.9, 11.7)*
207	*82.6 (114/138)*	*72.1 (98/136)*	*10.5 (0.7, 20.4)*
Response in the BPP Population			
069 Bacteriological	*86.8 (46/53)*	*82.4 (42/51)*	*4.4 (-9.4,18.3)*
207 Clinical	*80.9 (38/47)*	*87.0 (40/46)*	*-6.1 (-21.0, 8.8)*
Bacteriological	*63.8 (30/47)*	*68.3 (28/41)*	*-4.5 (-24.3, 15.3).*
Response in the BITT Population			
069 Bacteriological	*83.6 (46/55)*	*74.1 (43/58)*	*9.5 (-5.4, 24.4)*
207 Clinical	*81.3 (39/48)*	*82.4 (42/51)*	*-1.1 (-16.3, 14.1)*
Bacteriological	*62.5 (30/48)*	*60.8 (31/51)*	*1.7 (-17.4, 20.9)*

Additional findings in ABECB

In addition to the pivotal and supportive studies, the applicant submitted data from ancillary studies that characterized a variety of other parameters for the 5-day gemifloxacin regimen for ABECB. The table below describes the study designs for these three studies. The reader is referred to Appendix 1 for a more detailed discussion of these studies and the findings derived from them.

This review will discuss the proposed claim ("earlier eradication of *H. influenzae*") and then discuss the rest of the other findings in aggregate.

Table 6
Other Studies Evaluating Other Findings in Gemifloxacin ABECB Studies

	Study 105	Study 112	Study 139
Title	"A randomized, double-blind, double-dummy, multi-center, parallel group study to assess the investigate the pharmacokinetic and pharmacodynamic properties of 320mg oral Gemifloxacin once daily for 5 days versus 500mg Clarithromycin BID for 7 days in patients w/ABECB at risk of early recurrence"	"A randomized, double-blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Effectiveness and Health Economic Impact of Oral Factive TM (Gemifloxacin), 320mg Once Daily for 5 Days Versus Oral Clarithromycin 500mg Twice Daily for 7 Days for the Treatment of Acute Exacerbation of Chronic Bronchitis (ABECB)"	"A Health Economics Study to Assess the Cost effectiveness of Using Oral Gemifloxacin 320mg Once Daily for 5 days Versus Oral Clarithromycin 500mg Twice Daily for 7 Days in the Treatment of Acute Exacerbations of Chronic Bronchitis (ABECB)"
Comparators	Clarithromycin	Clarithromycin	Clarithromycin
Study dates	23 November 1999 to 26 July 2000	3 January 2000 to 19 December 2000.	20 November 1998 to 3 November 1999.
Study design	Randomized (1:1), multi-center, double-blind, double-dummy, parallel group	Randomized (1:1), multi-center, double-blind, double-dummy, parallel group	26 week double-blind, observational parallel/follow-on study to Study 068
Countries	Austria, Czechoslovakia, Poland, Sweden, United Kingdom, USA	Australia, Brazil, Canada, Ireland, Germany, Mexico, the Netherlands, Poland, United Kingdom, USA	USA , Canada
No. of centers	15	256	56
Randomized	169	1805	438
Age Gender	>40 male and female	>40 male and female	Same as 068
Inclusion criteria	Same as 207, except included outpatients	Same as principal studies	Same as 068
Objective	to determine : time to bacterial eradication time to recurrence relationship between PD and clinical outcome, bacterial eradication & time to bacterial eradication the effect on nasopharyngeal colonizing organisms the effect on levels of mediators of inflammation in sputum	to demonstrate superior clinical efficacy of gemifloxacin 320mg once daily for 5 days to that of oral clarithromycin 500mg twice daily for 7 days in the treatment of ABECB.	to demonstrate that treatment of ABECB with oral gemifloxacinm320mg once daily for 5 days compared with oral clarithromycin 500mg twice daily for 7 days in study SB-265805/068 resulted in fewer recurrences of ABECB, lower costs, less time off work and improved patient quality of life at the end of study SB-265805/068 and for an extended period afterwards
Unique aspect of study design	Evaluated patients at high risk, sophisticated cytokine, PK/PD, and MIC testing and analyses in a small study population.	Large population basis for pharmacoeconomic analyses	Follow-up to Study 068 at weeks 12 and 26 to measure economically relevant differences between treatments

Primary Efficacy Analysis	None, all exploratory	Time (in days) to next exacerbation of chronic bronchitis.	Proportion of patients resolved from first episode with no recurrence of ABECB (PP population) - recurrence free at day28-35, - recurrence free at Week 12 - recurrence free at week 26 - recurrence free at week 8 - recurrence free at Week 17 - recurrence free at Week 21 Quality of life (SGRQ)
Other Analyses	Clinical response EOT Clinical response FFUP Bacteriological response EOT Bacteriological response FFUP Change in inflammatory parameters Change in signs & symptoms Change in SGRQ response Change in % predicted FEV1 Change in sputum cytology Proportion with NP eradication on Day 1 for each of 4 organisms Proportion with NP eradication on Day 4 for each of 4 organisms Proportion with NP eradication on EOTx for each of 4 organisms Proportion with NP eradication on FFUP for each of 4 organisms MedianTime to bacterial eradication Time from the FFUP to next ABECB	Clinical response at Visit 2 Clinical response at Visit 3 Time to ABECB resolution Quality of life (SGRQ,12 visits) Use of resources and direct costs (medical) - # of hospitalizations and length of stay - # of unscheduled visits to the investigator or other physicians - # of prescribed drugs - # of diagnostic / other procedures Cost-effectiveness Direct costs (non medical) - care provided at home - patient out of pocket costs Indirect Costs :impact on work / productivity - cumulative # of days off work - cumulative # of days off usual activity - degree of impairment of work Survival analysis Recurrence according to steroid use By country steroid use By month disease severity By month smoking history	Proportion of patients resolved from first episode with no recurrence of ABECB (ITT population) - recurrence free at day28-35, - recurrence free at Week 12 - recurrence free at week 26 - recurrence free at week 8 - recurrence free at Week 17 - recurrence free at Week 21 Number of recurrences Differences in resource utilization - # of days of antibiotic Rx - # of hospital episodes and mean length of stay - # of physician visits - # of days of RTI related antibiotic Rx - # of RTI related hospital episodes and mean length of stay - # of RTI related physician visits - oxygen, ER and , diagnostic testing use Cost effectiveness Time off work/ productivity - cumulative # of days off work - cumulative # of days off usual activity - proportion of patients reporting different levels of impact on productivity

Rate of Bacterial Eradication and its Relevance in ABECB

The applicant makes an additional claim related to the rate of eradication of *H. influenzae* in patients with ABECB. The applicant's finding that gemifloxacin results in earlier bacterial eradication of *H. influenzae* compared to clarithromycin was based on unadjusted analyses in pivotal Study 068, and exploratory Study 105. In addition to the statistical issues relating to adjustment for multiple comparisons, there are questions regarding the clinical relevance of this finding given the small proportion of patients included in this analysis, the overall small proportion of bacteriologically evaluable patients in the pivotal studies, and the lack of correlation of clinical outcome to rate of eradication.

Of note, the analysis of time to bacterial eradication was based on a total of 24 patients with *H. influenzae* out of the 688 patients in the ITT population who fulfilled the inclusion criteria for ABECB in the pivotal studies. In this small subset of patients with *H. influenzae*, early eradication did not translate into clinical benefit over the comparator treated patients in whom eradication of *H influenzae* occurred at a later date. The following table describes the clinical course of these patients in Study 068, where clinical efficacy favored the comparator in the ITT and PP analysis at end of therapy, despite earlier eradication of *H influenzae* in the gemifloxacin treated patients. Similarly, the clinical outcomes at the follow up evaluation favored the comparator. Likewise, clinical outcomes in Study 105 were no different between gemifloxacin and comparator treated patients who had any bacterial pathogen or *H. influenzae* in their sputum.

Table 7
Impact of Earlier Bacterial Eradication on Clinical Outcome of Patients with ABECB

Clinical Outcomes in Study Populations	Gemifloxacin	Clarithromycin
	n/N (%)	n/N (%)
Study 068 Clinical Cure in patients with *H. influenzae*		
Per Protocol at End of Therapy	8/10 (80%)	10/12 (83%)
Per Protocol at Follow-up	8/10 (80%)	8/12 (67%)
Intent to Treat at End of Therapy	8/12 (67%)	10/12 (83%)
Intent to Treat at Follow-up	8/12 (67%)	8/12 (67%)
Intent to Treat at long-term Follow-up	6/12 (50%)	7/12 (58%)
Study 105 Sustained clinical success in patients with pathogens		
Bacterial Intent to Treat at End of Therapy	55 (83.3%)	45 (77.6%)
Bacterial Intent to Treat at Follow-up	38 (57.6%)	39 (67.2%)
Bacterial Intent to Treat at visit 1	30 (45.5%)	33 (56.9%)
Bacterial Intent to Treat at visit 2	25 (37.9%)	27 (46.6%)
Bacterial Intent to Treat at visit 3	20 (30.3%)	27 (46.6%)
Bacterial Intent at visit 4	19 (28.8%)	24 (41.4%)
Study 105 Sustained clinical success in patients with *H. influenzae*		
H. influenzae Intent to Treat at End Of Treatment	19 (82.6%)	24 (77.4%)
H. influenzae Intent to Treat at Follow-up	16 (69.6%)	21 (67.7%)

Limitations of Other Additional Findings

The applicant's other additional proposed findings for gemifloxacin in ABECB include: superior clinical efficacy in the ITT analysis, prolonged exacerbation free intervals and several findings related to efficacy in severe ABECB. The claims related to efficacy in severe ABECB include efficacy in patients requiring hospitalization, oral therapy obviating the need for intravenous therapy, earlier time to hospital discharge and reduction in hospitalization due to respiratory tract infections. These findings are limited by study design issues, lack of adjustments for multiple comparisons, and the unresolved clinical relevance of these findings in relation to overall outcomes in ABECB.

a) Applicant's proposed finding of superiority in the ITT analysis

The finding of superior clinical efficacy in the intent to treat analysis is derived from Studies 069 and 207 where the point estimates favored gemifloxacin and lower bounds excluded zero, with a value of 0.9 for study 068 and 0.7 for study 207. In the same studies, the primary analysis of clinical efficacy in the per protocol population and the secondary analysis of bacterial efficacy in the patients with pathogens show that gemifloxacin was non-inferior to the study comparators. The pivotal studies do not show superiority of gemifloxacin in clinical efficacy for any of the analytic populations. In addition, the applicability of this finding is limited by the fact that Study 207 was an open label non US study.

b) Applicant's proposed finding of comparable efficacy in severe ABECB

Two studies were submitted to the NDA that evaluate the efficacy of gemifloxacin in patients with more severe ABECB. These were studies 207, a supportive study and Study 105, an exploratory study in patients at higher risk for recurrence. The data from these 2 studies cannot be combined because the study design and objectives were different. In addition, only Study 207 prespecified a primary outcome and defined the statistical parameters for a determination of non-inferior clinical efficacy. While therapy in Study 207 was assigned randomly, the open label nature of the study could have introduced bias in the assessment of efficacy. However, this bias may have favored intravenous therapy rather than gemifloxacin. On the other hand, Study 105 was an exploratory study with more limited number of patients, but derives vigor from the double blind, double dummy study design.

Despite these limitations, however, both studies were designed a priori to select patients with severe ABECB based on similar objective criteria and provide insight on the efficacy of gemifloxacin in patients with more severe ABECB. Study 207 in particular provides efficacy data in a large proportion of patients already receiving corticosteroid therapy. However, since a stratified analysis of efficacy was not planned in the study, conclusions of efficacy in the subset receiving corticosteroids would be of limited significance.

Patients in these studies were older, had more frequent exacerbations of ABECB, more often required oxygen and corticosteroids at baseline, and more often had lower FEV1 than the patients that were enrolled in the pivotal studies of ABECB.

Table 8 Efficacy of Gemifloxacin in Severe ABECB: Studies 207 and 105

Study element	Study 207		Study 105	
Design	Open label randomized efficacy study		Randomized double blind, double dummy experimental study	
Additional inclusion criteria	Hospitalised patients able to tolerate oral therapy		In or Outpatient	
	Had one of more of the following: FEV 1 <50% of predicted, age >65 years, ≥4 episodes of ABECB in the past year requiring treatment with an antibacterial agent, cardiorespiratory comorbidity or 3 comorbidity markers from w/in cardiovascular, musculoskeletal, central nervous system, endocrine, hematologic or hepatic systems			
Treatment	Treatment Group A: Oral Gemifloxacin 320mg OD X 5 days. Treatment Group B: IV Ceftriaxone (1g, OD up to 3 days), then oral cefuroxime (500mg, BID, to a maximum of 7 days).		Treatment Group A: Oral gemifloxacin 320mg OD X 5 days & oral clarithromycin placebo BID X 7days. Treatment Group B: Oral clarithromycin 500mg BID X 7 days and oral gemifloxacin placebo OD X 5 days.	
Primary Efficacy Parameter	Clinical response in the per protocol population at follow-up		None, end of therapy & follow-up efficacy were secondary	
Response evaluation	Success: Sustained improvement or resolution of signs and symptoms of ABECB for patients who were clinical successes at the End of therapy visit, such that no additional antibacterial therapy is indicated for ABECB.			
Study sites	46 centers in 8 countries: Belgium (2 centers), Holland (7 centers), Hungary (6 centers), Italy (14 centers), Mexico (1 center), Poland (9 centers), South Africa (4 centers) and the United Kingdom (3centres),		15 centers in 6 countries: Austria (2 centers), Czech Republic (2centers), Poland (2 centers), Sweden (4centers), United Kingdom (2 centers), & United States (3 centers)	
Demographic Characteristics (ITT)	*Gemifloxacin N =138*	*IV to Oral N =136*	*Gemifloxacin N = 83*	*Clarithromycin N = 80*
Male gender	*103 (74.6)*	*90 (66.2)*	*47 (56.6)*	*43 (53.8)*
Age in years, mean (SD)	*68.1 (9.9)*	*67.1 (10.3)*	*64.1 (9.5)*	*63.4 (9.9)*
Duration of CB in years, mean	*12.6 (9.5)*	*11.8 (9.6)*	*14.6 (11.9)*	*15.8 (11.3)*
*Patients w/ > 4 exacerbations** n (%)*	*40 (29.0)*	*46 (33.8)*	*30 (36.1)*	*27 (33.8)*
Use of Supplemental Oxygen, n (%)	*34 (24.6)*	*33 (24.3)*	*5 (6.0)*	*5 (6.3)*
Use of Systemic Steroids, n (%)	*65 (47.1)*	*61 (44.9)*	*32 (38.6)*	*16 (20.0)*
>30 pack-years smoking history, n (%)	*	*	*57 (68.7)*	*49 (61.3)*
Smoked Regularly in Last Month, n(%)	*	*	*41 (49.4)*	*38 (47.5)*
Anthonisen Stage 2 *Anthonisen Stage 3*	*120 (87.0)* *18 (83.0)*	*124 (91.2)* *12 (8.8)*	*70 (84.3)* *13 (15.7)*	*71 (88.8)* *9 (11.3)*
FEV1 <50% of predicted, n (%)	*127 (92.00)*	*110 (80.9)*	*51 (61.4)*	*38 (47.5)*
Clinical Success at End of therapy (ITT)	*127/138 (92.0)*	*120/136 (88.2)*	*68/83 (81.9)*	*61/80 (76.3)*
Clinical Success at End of Therapy (PP)	*122/126 (96.8)*	*115/122 (94.3)*	*	*
Clinical Success at Follow-up (ITT)	*114/138 (82.6)*	*98/136 (72.1)*	*51/83 (61.5)*	*54/80 (67.5)*
*Clinical Success at Follow-up (PP)****	*105/126 (86.8)*	*91/122 (81.3)*	*	*
Bacterial Success at End of therapy (ITT)	*39/48 (81.3)*	*42/51 (82.4)*	*42/66 (63.6)*	*30/58 (51.7)*
Bacterial Success at End of Therapy (PP)	*38/47 (80.9)*	*40/46 (87.0.)*	*	*
Bacterial Success at Follow-up (ITT)	*30/48 (62.5)*	*28/41 (68.3)*	*26/66 (39.4)*	*20/58 (34.5)*
Bacterial Success at Follow-up (PP)	*30/48 (62.5)*	*31/51 (60.8)*	*	*

** not reported **requiring antibiotic therapy in the last year ***primary analysis of efficacy*

The clinical efficacy in both treatment arms in Studies 105 and 207 were generally lower than those reported in the pivotal studies for both treatment arms, with primary clinical success rates in the pivotal studies in the low 90's or upper 80's, compared to 61.5% and 67.5% for gemifloxacin and comparator in Study 015 and 86.8% and 81.3% in Study 207. Compared to the CAP studies where efficacy in patients with more severe CAP had outcomes similar to those with milder disease, the ABECB studies appear to have internal validity regarding the severity of ABECB in the populations studied.

However, it is not clear why the efficacy rates in Study 105 are lower than those found in Study 207, particularly as Study 105 enrolled both an in and an outpatient population, compared to Study 207 where the population was felt to need hospitalization. One potential confounder is the fact that a higher proportion of patients in Study 207 was receiving corticosteroid therapy. One other larger issue is the validity of the criteria used to define the populations studied as indeed having more severe ABECB, or as being predictive of the need for hospitalization (Study 207) or of predicting earlier exacerbation (Study 105).

Nevertheless, several observations from these studies support the notion that gemifloxacin provides benefit similar to the comparator in patients with severe ABECB and lends credence to the fact that patients described in this study may represent a population that benefits from antibiotic therapy. These include the observation that efficacy in the PP and ITT populations trended in the same direction, as did bacterial eradication in these populations, and that the rates of clinical and bacteriologic success parallel each other at the two time points of assessment (i.e. greater clinical relapses at follow-up correlating with decreased bacteriologic efficacy at follow-up).

c) Applicant's proposed finding of comparable efficacy to parenteral therapy in hospitalized ABECB obviates the need for intravenous therapy

In the applicant's background package provided to the Anti-Infective Advisory Committee, the applicant extends the finding of non-inferior efficacy of gemifloxacin to parenteral therapy in study 207, by claiming that oral gemifloxacin therapy obviates the need for parenteral therapy and hospitalization, allowing greater mobility in the elderly. While clinical efficacy of gemifloxacin was found to be non-inferior to parenteral therapy in this study, it is important to note that 207 was an open label non-US study, raising the question of applicability of the findings to an analogous hospitalized US population. Furthermore, this study enrolled patients w/ severe ABECB who were able to tolerate oral medications, limiting the applicability of these findings to the wider population of all hospitalized ABECB patients, as patients who are able to tolerate oral therapy may not necessarily require parenteral therapy nor hospital care.

d) Applicant's proposed finding of earlier time to discharge in hospitalized patients

The applicant also shows that gemifloxacin treated patients were discharged a mean of 0.5 days earlier than patients that received parenteral therapy. This difference in mean time to discharge could be accounted for by the time required to insert & then remove intravenous access in the patients that received parenteral therapy. No difference was found in the primary outcome of clinical efficacy. Related outcomes

such as rate of symptom resolution & indirect treatment costs were no different between treatments. Furthermore, this analysis was only marginally significant using a Wilcoxon test (p=0.04), not significant using a log rank test (p=0.16) & hazard ratio was not significantly different than 1.

e) Applicant's proposed finding of longer time to next exacerbation

Time to next exacerbation was evaluated in three studies. The findings from 2 of these studies are limited by the failure to adjust for multiple comparisons or the failure to pre-specify the methodology for adjustment. Nevertheless, were the analyses statistically significant, the findings were contradictory, with Study 139 trending favorably for gemifloxacin, and Study 105 favoring the comparator. In Study 112 where this analysis was the primary outcome of interest and required no statistical adjustment, time to exacerbation with gemifloxacin was not significantly different from comparator.

Table 9
Unadjusted Analyses of Proportion of Patients who Remain Recurrence - Free in Studies 139, 112 and 105

Study	*Visit/Call*	*Gemifloxacin*	*Comparator*	*P-value*
139	*Visit 2 (week 4,5)*	*176/202 (87.1)*	*173/214 (80.8)*	*0.081*
	Call 1 (week 8)	*165/195 (84.6)*	*159/197 (80.7)*	*0.039*
	Visit 3 (week 12)	*148/183 (80.9)*	*131/176 (74.4)*	*0.143*
	Call 2 (week 17)	*135/179 (75.4)*	*118/176 (67.0)*	*0.084*
	Call 3 (week 21)	*117/160 (73.1)*	*97/156 (62.2)*	*0.110*
	Visit 4 (week 26)	*120/169 (71.0)*	*100/171 (58.5)*	*0.016*
112	*(week 17-20)*	*595/903 (65.9)*	*586/896 (64.5)*	*0.827*
105	*(week 11)*	*33/83 (39.8)*	*38/80 (47.5)*	*0.319*

f) Applicant's proposed finding of reduction of respiratory tract related hospitalization

Respiratory tract related hospitalization was evaluated in Studies 105, 139 and 112, but the applicant presents only the results from Study 139 in the NDA. The finding of reduced hospitalization in gemifloxacin-treated patients was not adjusted for multiple comparisons and other related outcomes, (such as the number of days of respiratory tract related antibiotic therapy, number of respiratory tract related physician visits, number of recurrences and quality of life measures) were no different between treatment arms and do not support this finding.

Review of Safety

A more detailed discussion of the safety of gemifloxacin in ABECB is presented in Dr. John Power's review of the original NDA studies and Dr. Maureen Tierney's review of the consolidated clinical studies submitted following the non-approval of the original NDA. This review will present the overall proportions of select key safety indicators in the gemifloxacin and comparator treated patients, the proportions of rash in patients younger than or older than 40 years of age, QTc data obtained specifically in 2 ABECB studies, and end with a discussion of select adverse events notable in some of the ABECB studies.

Overall safety

Overall safety in ABECB patients receiving the proposed label dose of gemifloxacin did not differ from that of the comparators in the proportions of patients with adverse events, serious adverse events, discontinuations due to adverse events and deaths.

Table 10
Proportions of Patients with ABECB with Reported Clinical Adverse Events

Patients with reported clinical adverse events	Gemifloxacin N=2601		Comparators N=2548	
	n	%	n	%
Any adverse event	1096	42.1	1147	45.0
Serious adverse events	90	3.41	94	3.69
Discontinued due to adverse events	80	3.08	102	4.00
Deaths	25	0.96	18	0.73

The most common reported adverse events were headache, nausea and diarrhea. Other events associated with quinolone use such as arthralgia and tendinitis were infrequent (less than 1%). None of the deaths were reported to be drug related.

Rash

A total of 2284 patients with ABECB received 320 mg of gemifloxacin for 5 days and 563 received therapy for longer than 5 days. Females comprised 46.5% (1062/2284) and 41% (233/563) of these respective patient subgroups. Only 41 patients of the 2284 who received the proposed gemifloxacin label dose and duration were under 40 years of age (< 0.2%) and no rashes occurred in these patients (0 of 22 females and 0 of 19 males).

Rash rates were clearly higher for patients that received longer than 5 days of therapy, regardless of age or sex. However, rates of rash in females were clearly higher for females (10/233 or 4.3%) than for males (7/330 or 2.1%). Notable, however is the fact that the rates of rash in males under 40 (5/19 or 20%) was comparable to that of females under 40 years (2/12 or 16.7%), although the number of patients were very small in these subgroups.

Table 11
Age and Sex Rates of Rash in ABECB Phase III Trials *

	Gemifloxacin				*Comparators*			
Duration of Treatment	*≤5 days*		*> 5 days*		*≤ 7 days*		*> 7 days*	
	Total	*n (%)*	*Total*	*n (%)*	*Total*		*Total*	*n (%)*
Both, all ages	*2284*	*27 (1.2)*	*563*	*17 (3.0)*	*2522*	*21 (0.8)*	*69*	*0*
Both, < 40 years	*41*	*0*	*17*	*3 (17.6)*	*55*	*0*	*4*	*0*
Both, ≥ 40 years	*2243*	*27 (1.2)*	*546*	*14 (2.6)*	*2467*	*21 (0.9)*	*65*	*0*
All Females	*1062*	*16 (1.5)*	*233*	*10 (4.3)*	*1157*	*15 (1.3)*	*26*	*0*
Females, < 40 years	*22*	*0*	*12*	*2 (16.7)*	*32*	*0*	*2*	*0*
Females, ≥ 40 years	*1040*	*16 (1.5)*	*221*	*8 (3.6)*	*1125*	*15 (1.3)*	*24*	*0*
All Males	*1222*	*11 (0.9)*	*330*	*7 (2.1)*	*1365*	*6 (0.4)*	*43*	*0*
Males, < 40 years	*19*	*0*	*5*	*1 (20.0)*	*23*	*0*	*2*	*0*
Males, ≥ 40 years	*1203*	*11 (0.9)*	*325*	*6 (1.8)*	*1342*	*6 (0.4)*	*41*	*0*

**From the Applicant's Table 54 Briefing Document to the Anti-Infectives Advisory Committee*

One study was notable among the ABECB studies because of the greater frequency of reported rashes and the more detailed representation of rashes in the study report. This was Study 112, a larger, multicenter comparative study conducted in 10 countries in Australia, Brazil, Canada, Ireland, Germany, Mexico, the Netherlands, Poland, UK and the USA. The US sites contributed the majority of patients (452/903 in the Gemifloxacin and 447 or 896 clarithromycin treated patients) in this study, possibly accounting for the increased reporting of adverse events in this study. Overall, 3.1% of the gemifloxacin treated group and 2.7% for the clarithromycin treated group was reported to have a dermal adverse event, including rash.

Table 12
Number (%) of Patients with AEs Related to Skin Rash in Study 112

	Treatment group			
	Gemifloxacin		Clarithromycin	
	N=903		N=896	
Preferred term	n	(%)	n	(%)
Any AE of skin and appendages	28	(3.1)	24	(2.7)
Dermatitis	2	(0.2)	1	(0.1)
Pruritus	6	(0.7)	3	(0.3)
Rash	4	(0.4)	2	(0.2)
Rash erythematous	8	(0.9)	4	(0.4)
Rash maculopapular	0		2	(0.2)
Urticaria	2	(0.2)	2	(0.2)

Source: SPONSOR's Study 112 Summary Report Section 13, Table 12.05; Appendix D, Listing D.01.

The majority of rashes reported as adverse events in both treatment groups of Study 112 occurred in women. Most were mild and required no intervention. Two patients withdrew from therapy, one from each study arm. Ten of 12 gemifloxacin rash events were attributed by the investigator to study medication, compared to 4 of 9 rash events in the comparator. None of the gemifloxacin rashes were maculopapular, none were considered severe, all but one resolved at end of therapy, 4 required therapy and one resulted in withdrawal from study.

Table 13
Details on the Reported Rash Adverse Events In Study 112

AE/Patient#	Age (yr)	Sex	Onset* (days)	Duration days)	Outcome	Intensity	Relation to Rx	Therapeutic adjustment	Withdrawn
Gemifloxacin Rash									
112.001.36289	51	F	2	4	resolved	mild	suspected	n	n
112.203.38463	46	F	8	3	resolved	mild	unlikely	n	n
112.729.35594	80	M	10	3	resolved	mild	suspected	n	n
112.735.35630	61	F	7	cont	ongoing	mild	unlikely	y	n
Rash erythematous									
112.047.38234	70	M	2	3	resolved	mild	unlikely	n	n
112.114.36023	65	F	16	7	resolved	mild	unrelated	y	n
112.215.38848	67	F	22	9	resolved	mild	unrelated	n	n
112.217.37780	68	F	34	1	resolved	mod	suspected	n	n
112.225.37759	49	M	2	3	resolved	mild	suspected	n	y
112.229.37733	52	F	5	3	resolved	mild	suspected	n	n
112.508.35670	76	F	14	2	resolved	mod	probably	y	n
112.740.35357	46	M	1	2	resolved	mild	Suspected	y	n
Clarithromycin Rash									
112.105.37996	46	F	4	7	resolved	sev	Probably	y	y
112.134.38368	77	F	9	cont	ongoing	mod	Probably	n	n

Rash erythematous									
112.067.38117	58	F	8	2	resolved	mild	unlikely	n	n
No detail available			20	4	resolved	sev	unrelated	n	n
112.103.37624	53	M	2	4	resolved	mild	suspected	n	n
112.203.38493	52	F	11	38	resolved	mild	unrelated	y	n
112.551.35673	74	F	6	39 h	resolved	mod	unrelated	n	n
Rash maculopapular									
112.046.38768	69	F	2	3	resolved	mild	suspected	n	n
112.066.37894	52	F	14	48 h	resolved	mild	unrelated	n	n

Table Source: SPONSOR'S Table 32, Summary Report, Study 112 Appendix B, Listing B.05; Appendix D, Listing D.01.
* Number of days relative to start date of study medication.

It is notable that all the patients that developed the rashes were all above 40 years, consistent with the known epidemiology of ABECB. It is reassuring that while the rates of rash appear greater with gemifloxacin, there is no marked difference in severity nor treatment discontinuations between the two arms.

QTc changes

Two studies included EKG monitoring in the safety analysis of patients with ABECB, Study 212, a pivotal study and Study 105 an exploratory study. In Study 212, paired QTc data were obtained from 89.4% of patients (gemifloxacin: 86.8% or 158/182; levofloxacin: 92.1% or 164/178. One patient in each treatment group had a change in QTc that was outside of the normal range. After adjusting for age and sex there was no statistically significant difference between the treatment groups in the change in QTc from off-therapy to on-therapy. In Study 105, 24 gemifloxacin and 23 clarithromycin treated patients had paired ECGs. No patient had a QTc value out of range at screening or a QTc value or change in QTc that was out of range on-therapy, including 11 patients in the gemifloxacin treatment group and 10 patients in the clarithromycin treatment group with risk of underlying cardiac abnormality. Six gemifloxacin treated patients and 3 clarithromycin treated patients had treatment-emergent ECG abnormalities. None had an AE associated with the abnormal ECG finding and none withdrew from the study as a result of the treatment emergent abnormal finding. However, one patient, in the gemifloxacin treatment group, had a treatment-emergent ECG abnormality on therapy related to QT interval. This was a 53-year-old female with a history of hypertension, (Patient 105.022.34001), who had a normal ECG at screening; and an on-therapy increased QT interval with a baseline QTc of 423 msec at screening and an end of therapy QTc of 470msec (47 msec increase). The patient received no concomitant medications known to prolong the QT interval. There were no clinical events associated with this increased QTc and the patient continued in the study.

CPK elevations

Among the 10 ABECB studies, CPK elevations was noted more frequently in Studies 068 and 112. This may be due in part to the fact that these studies enrolled the greatest number of patients from US investigative sites, where clinical adverse event reporting or routine laboratory testing norms may be different from the non US sites. This adverse event was therefore evaluated in Studies 068 and 112 in greater detail.
CPK elevations in Study 112:
1.Reported adverse events related to elevated CPK were summarized from the CRTs in the electronic database. A clinical adverse event of elevated CPK was reported in 15 gemifloxacin treated patients and 8 comparator treated patients. It is important to point out that the majority of these CPK elevations were present at baseline. Of these,

5 occurred following start of therapy in the gemifloxacin treatment group, compared to 1 in the clarithromycin treatment group (shaded in the following line listing). Of these, 2 in the gemifloxacin arm had a CPK elevation over 1000 (darkly shaded). One of these 2 patients was concomitantly receiving a cholesterol lowering agent and had a severe event, whereas the other with no confounding factors was considered drug related and of moderate severity. None of these events required withdrawal from study, all occurred at least a week after start of therapy and at least 4 days after the last dose. All events were in males over 50 years of age. None of these patients had a concomitant myocardial adverse event.

Line Listing of patients w/ CPK elevations in Study 112 reported as CLINICAL Adverse Events

ID	Therapy	Race	Sex	Age	Severity	Drug Related	Onset First	Time* Last	Event Rx	Required W/drawal	Confounder
38232	Gemifloxacin	White	Female	56	Mil	Not	0	-7	N	N	
36092	Gemifloxacin	White	Male	56	Mil	Not	0	-7	N	N	
38028	Gemifloxacin	Black	Male	45	Mod	Not	0	-7	N	N	
37619	Gemifloxacin	White	Female	47	Mil	Not	0	-7	N	N	
35896	Gemifloxacin	Black	Male	41	Mil	Not	0	-6	N	N	
37759	Gemifloxacin	White	Male	49	Mil	Not	0	-2	Y	N	
35219	Gemifloxacin	Black	Male	51	Sev	Not	0	-6	N	N	
35732	Gemifloxacin	White	Male	52	Mod	Not	-3	-9	N	N	
39552	Gemifloxacin	White	Male	71	Mod	Not	0	-7	N	N	
37710	Gemifloxacin	Black	Male	64	Mod	Not	10	4	N	N	
35973	Gemifloxacin	White	Male	64	Mil	Not	14	6	N	N	meds
36188	Gemifloxacin	White	Male	78	Mil	Not	21	14	N	N	
37959	Gemifloxacin	White	Male	54	Mod	Sus	18	12	Y	N	
39857	Gemifloxacin	White	Male	71	Sev	Not	14	8	N	N	meds
39969	Gemifloxacin	White	Male	70	Mod	Not	17	11	N	N	
38038	Clarithromycin	Black	Female	55	Mod	Not	0	-6	N	N	
38061	Clarithromycin	White	Female	66	Mil	Not	0	-7	N	N	
38519	Clarithromycin	White	Male	54	Mil	Not	0	-6	N	N	
35947	Clarithromycin	White	Female	50	Mil	Not	0	-6	N	N	
36164	Clarithromycin	White	Female	55	Mod	Not	0	-7	N	N	
37730	Clarithromycin	White	Female	65	Unk	Not	0	-6	N	N	
37776	Clarithromycin	White	Male	68	Mil	Not	0	-6	N	N	
36514	Clarithromycin	White	Female	53	Mod	Sus	14	8	N	N	

*number of days in relation to treatment dose

Three patients had an adverse event labeled as myopathy or myositis. The event in the gemifloxacin treated patient occurred well beyond the treatment period, whereas 2 clarithromycin treated patients had myositis occur more proximate to therapy. One of these patients, a clarithromycin treated patient, was felt by the investigator to have myositis related to drug.

Line Listing of patients with myopathic adverse events in Study 112

ID	Therapy	Race	Sex	Age	Severity	Drug Related	Onset First	Time** Last	Event Rx	Required W/drawal	Confounder
40157	Gemifloxacin	White	Male	58	Mod	Not	123	116	Y	N	
36514	Clarithromycin	White	Female	53	Mod	Sus	14	8	N	N	
35211	Clarithromycin	White	Male	40	Mil	Not	9	3	Y	N	

*number of days in relation to treatment dose

2. The data tables summarizing CPK results were then reviewed to determine
a) any elevations over the upper limit of normal,
b) any elevation meeting the F2/F3 threshold

c) any elevation over 1000 IU/l.
An elevation of CPK of any magnitude above the upper limit of normal was reported in 106/908 (11.7%) gemifloxacin treated patients compared to 97/847 (11.5%) clarithromycin treated patients. However, the incidence of F2F3-flagged values for CPK at Visit 2 was low (5 patients or 0.6% in the gemifloxacin group and 4 patients or 0.5% in the clarithromycin group). Of these, 3 patients in the gemifloxacin group and one in the clarithromycin group had adverse events related to the CPK abnormality. These patients represent 0.3% of the gemifloxacin treated patients (3/908) and 0.1% (1/847) of the clarithromycin treated patients.
Patient 112.119.35973, was a 64-year-old man treated with gemifloxacin, who had mild CPK elevations beginning on Day 14 and continuing through the end of the study. The AE was not considered related to study medication, did not require corrective therapy nor lead to study withdrawal from the study.
Patient 112.219.37959, was a 54-year-old man treated with gemifloxacin, who had moderate CPK elevations beginning on Day 18 and lasting 3 days. This was suspected to be related to study medication and required corrective therapy. The AE resolved, and the patient completed the study.
Patient 112.588.39857, was a 71-year-old man treated with gemifloxacin, who had a severe AE of elevated CPK on Day 14 continuing to the end of study. This patient was receiving a cholesterol-lowering agent as concomitant therapy. The AE was considered unrelated to study medication, did not require corrective treatment or withdrawal from the study, and the patient completed the study.
Patient 112.175.36514,was a 53-year-old woman treated with clarithromycin, who had an AE of moderately elevated CPK on Day 14 and lasting 6 days. The AE was considered related to study medication, did not require corrective treatment or withdrawal from the study.

CPK elevations and the reported adverse events that accompanied these elevations did not seem to occur more frequently in the gemifloxacin treatment arm than in the comparator treatment arm in Study 112. Moreover, a number of these CPK elevations were present at baseline and could not be attributed to study drug therapy. In addition, while these patients were older and had more frequent comorbidities, a myocardial event was not reported for these patients and did not appear to confound these events. Systemic viral illnesses such as influenzae could be associated with myopathy and often presents late in the course of the disease, however, the clinical presentation is rather distinct from the events described in Study 112. One potential confounder for myopathy in patients with ABECB is that caused by corticosteroid therapy. In study 068, the use of corticosteroids in relation to onset time of the CPK elevation was evaluated in addition to the above evaluation strategy.

Following is a line listing of patients in Study 068 reported to have a clinical adverse event of CPK elevation. None of these patients are reported to have a muscular adverse event.

NDA 21-158 Factive (gemifloxacin mesylate)
Addendum to MOR of Acute Bacterial Exacerbation of Chronic Bronchitis

Rx*	ReportedAE	ID	Age/sex	AE Serious	Needed Therapy	Study W/drawal	AE Severity	Relationship to Rx	Outcome	Onset Time	Duration	Relation to First	Dose Last	Confounding Meds
Gemi	ELEVATED CPK	14585	53Female	No	No	No	Mild	Not related	Ongoing	Pre Treatment	Continuing	0	-7	S (t)
Gemi	HIGH CPK	14693	69Female	No	No	No	Mild	Not related	Resolved	Pre Treatment	4 Days	0	-6	S(i)
Gemi	INCREASED CPK	14510	62Male	No	No	No	Severe	Not related	Ongoing	Pre Treatment	Continuing	0	-6	S (n)
Gemi	ELEVATED CPK	14469	49Male	No	No	No	Mild	Not related	Resolved	Pre Treatment	49:22	0	-6	S (i)
Gemi	TOTAL CPK 258U/L	20997	54Male	No	No	No	Mild	Not related	Resolved	Pre Treatment	47:15	0	-6	S (t,i), LLA
Gemi	ELEVATED CPK	14049	48Male	No	No	No	Moderate	Unlikely	Resolved	On Treatment	5 Days	3	-3	
Gemi	INCREASED CPK	14539	53Male	No	No	No	Mild	Suspected	Resolved	On Treatment	7 Days	2	-4	S (n)
Gemi	ELEVATED CPK	14158	43Male	No	No	No	Moderate	Suspected	Resolved	On Treatment	4 Days	3	-4	
Gemi	ELEVATED CPK	14251	47Female	No	No	No	Mild	Not related	Ongoing	On Treatment	Continuing	0	-9	S (o)
Gemi	ELEVATED CPK	14825	47Male	No	No	No	Moderate	Not related	Ongoing	On Treatment	Continuing	0	-7	
Gemi	ELEVATED CPK	14048	43Female	No	No	No	Severe	Not related	Resolved	Post Treatment	20 Days	9	3	S (i)
Gemi	ELEVATED CPK	14106	63Male	No	No	No	Moderate	Probable	Resolved	Post Treatment	9 Days	10	4	
Clari	CPK 336 U/L	21096	63Female	No	No	No	Moderate	Not related	Ongoing	Pre Treatment	Continuing	0	-7	
Clari	INCREASED CPK	14129	76Male	No	No	No	Moderate	Not related	Ongoing	On Treatment	Continuing	0	-2	
Clari	HIGH CPK	14579	50Male	No	No	No	Moderate	Not related	Resolved	On Treatment	3 Days	0	-7	
Clari	CPK,TOTAL=509	14197	75Male	No	No	No	Mild	Suspected	Resolved	On Treatment	6 Days	3	-3	
Clari	ELEVATED CPK	14382	47Male	No	No	No	Mild	Suspected	Ongoing	On Treatment	Continuing	2	-6	S (o)
Clari	CPK 384 U/L	21081	52Male	No	No	No	Moderate	Unlikely	Resolved	On Treatment	9 Days	2	-5	
Clari	CPK 72U/L	14129	76Male	No	No	No	Severe	Unlikely	Resolved	Post Treatment	4 Days	3	1	
Clari	ELEVATED CPK	14702	55Female	No	No	No	Mild	Probable	Ongoing	Post Treatment	Continuing	10	4	S (i)
Clari	INCREASED CPK	14439	59Female	No	No	No	Mild	Suspected	Resolved	Post Treatment	6 Days	10	4	S (i)

Gemi=gemifloxacin, Clari=clarithromycin S= costicosteroids, I=inhalational, T=topical, o=oral, n=nasal, LLA=lipid lowering agent

CPK elevations were reported as clinical adverse events in 12/340 (3.5%) gemifloxacin and in 9/304 (2.9%) comparator treated patients. None of these events was serious. None needed therapy nor resulted in study withdrawal. 7 of the 12 gemifloxacin treated patients developed the CPK elevation on therapy or follow-up, varying in onset time from 2-10 days from the first dose of study drug, compared to 8 of 9 comparator treated patients, with a similar onset time. One event in each treatment arm was considered severe; both judged unrelated to study drug. All patients with baseline CPK elevations in the gemifloxacin treatment arm received corticosteroids, as did 3 of the 7 treatment emergent events.

The proportion of patients with a laboratory adverse event of elevated CPK was next evaluated. 3 of 340 (0.9%) gemifloxacin treated patients had an F2F3 flag for elevated CPKs compared to 4 of 304 (1.4%) comparator treated patients. One of the three gemifloxacin treated patients (ID 14048) was on maintenance inhalational corticosteroid therapy and had elevated baseline CPK values (559 U/L) that slightly declined (494 U/L) on follow-up. Two of the 4 comparator treated patients with flagged CPK elevations were receiving maintenance inhalational corticosteroids (ID 15303 and 14914, neither reported as a clinical AE, with maximal CPK elevations of 828 U/L and 2185 U/L, respectively). The proportion of patients with unconfounded flagged CPK elevations was similar between the two treatment arms, (2/340 or 0.6% for gemifloxacin and 2/304 or 0.7% for clarithromycin). One of these patients in either treatment arm was also reported as a clinical event.

The proportion of patients with flagged CPK elevations also reported as clinical events was 0.3% and 0.1% for gemifloxacin and clarithromycin, respectively, in study 112 and 0.3% for both treatment arms in study 068. Although the overall rates of CPK elevations are higher in these 2 studies than those observed in the rest of the other ABECB studies, the clinically significant events were infrequent and were similar between treatment arms. CPK elevations have not been described as a class effect for the fluoroquinolones. Elevation of CPK is not noted in the adverse event section of the labels for ciprofloxacin, moxifloxacin, gatifloxacin, levofloxacin and ofloxacin and does not indicate that this was a frequent 1-%) adverse event. However, rhabdomyolysis was noted as an adverse event in the clinical trials leading to the registration of levofloxacin and is listed as a postmarketing adverse event for ofloxacin. The emergence of clinically significant CPK elevations and rhabdomyolysis following gemifloxacin therapy should be closely evaluated in the postmarketing phase.

Summary and Risk-Benefit Assessment:

The comparative studies that enrolled over 2000 gemifloxacin treated patients find that gemifloxacin are non-inferior to its comparators in the treatment of ABECB. The finding of non-inferior clinical efficacy in the 3 pivotal studies is supported by similar findings in the 2 supportive and 3 ancillary studies of ABECB. Of note, the lower bounds of the 95% confidence intervals in the population of interest in the pivotal studies in this NDA were all within -5 percentage point of zero. While this may fulfill the current margins for non-inferiority derived from the 13% attributable benefit for antimicrobial therapy described in the original placebo controlled study by Anthonisen [1], questions remain regarding the true magnitude of the benefit of antimicrobial therapy for this indication. Nonetheless, the analyses in the other populations buttress the findings in the primary efficacy analysis. The outcomes in the ITT populations as well as the outcomes in the patient populations with bacterial pathogens generally supported the per protocol analyses. Finally the finding that gemifloxacin was efficacious in patients considered to have more severe ABECB lends further confidence to the efficacy findings for this anti-infective.

Based on the ABECB studies submitted to the NDA, gemifloxacin safety and tolerability appears to be similar to other approved therapies. The population studied in the clinical trials, however, consisted generally of older patients, and cannot predict the safety of gemifloxacin in the broader population likely to see use in the community. This is of particular concern regarding the rash adverse event, which although seen in only 1.2% of the overall population studied, is likely to be seen more frequently when the drug is used in the community, based on the utilization data presented by the applicant. Furthermore, there is a potential that the rash may have been attenuated by concomitant therapy with corticosteroid or antihistamine therapy in the patients with ABECB in the clinical trials. In addition to the concerns regarding rash, patients with ABECB are also likely to have other factors that may predispose them to the hepatic and QT related effect of gemifloxacin. ABECB patients are likely to be older, have frequent cardiac, hepatic or other co-morbid conditions that can increase their

[1] *Anthonisen NR, Manfreda J, Warren CPW, et al. Antibiotic therapy in exacerbations of chronic obstructive lung disease. Ann Intern Med 106:196-204. 1987*

susceptibility to these events. The applicant proposes unit dose packaging and patient and provider education regarding these events, as means to mitigate these risks.
Nevertheless, the question remains regarding the size of treatment attributable benefit for the indication ABECB, as well as the population in whom the benefit is measurable. The Advisory committee that evaluated gemifloxacin suggested that until the Anthonisen study is duplicated and further validated by another placebo controlled trial, the current standards for approval of antibiotics must hold.
An issue that needs to be addressed in assessing the risk benefit of gemifloxacin is the potential that a patient is labeled quinolone allergic on the basis of a rash or becomes cross-sensitized to subsequent quinolones. While there is currently no dearth of alternatives for the treatment of ABECB, the quinolone antimicrobials comprise a significant proportion of the treatment alternatives for ABECB, and the development of allergy or cross-sensitization would restrict the alternatives for this indication. Furthermore, Elimination of the quinolones as a therapeutic alternative may impact ABECB, more than it would CAP, given that patients with ABECB experience multiple recurrences requiring repeated antimicrobial exposures.

Proposed Labeling:

Following are sections of the sponsor's proposed label relevant to the ABECB indication with the MO's proposed revisions (alternative text underlined).

" INDICATIONS AND USAGE

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NDA 21-158 Factive (gemifloxacin mesylate)
Addendum to MOR of Acute Bacterial Exacerbation of Chronic Bronchitis

Recommendation:
The MO recommends approval for the indication ABECB *caused by Streptococcus pneumoniae; Haemophilus influenzae; Haemophilus parainfluenzae;* and *Moraxella catarrhalis.* The MO does not recommend that the additional claim of early eradication of *H. influenzae* be included in the drug label.

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Append distribution list

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ON ORIGINAL

Appendix 1: ABECB section of the FDA Backgrounder for the March 4, 2003 Anti-Infective Advisory Committee Meeting

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

The Applicant presents data from 11 clinical studies in ABECB to support the safety and efficacy of gemifloxacin in the treatment of ABECB. Eight of the studies used a dose of 320 mg po qd for 5 days, two studies used a dose of 320 mg po qd for 7 days, and one dose ranging study that was performed early in the clinical development program used a treatment duration of 10 days. In the review of the Applicant's original submission from December of 1999, the Agency concurred with the applicant's conclusion that gemifloxacin was efficacious for the treatment of ABECB at a dose of 320 mg po qd for 5 days, however there were unresolved safety issues and questions regarding the overall risk benefit for this indication. In the sections that follow, the principle and supportive studies will be discussed followed by a discussion of the proposed claims made by the sponsor.

Applicant's Proposed Labeling Claim

The Applicant's Indication for ABECB is as follows:

[ ]

Acute Bacterial Exacerbation of Chronic Bronchitis: Principal Studies

The three principal studies (Study 068, 070, 212) were randomized, double blind, double-dummy, parallel group studies, that compared the clinical and microbiological efficacy and safety of oral gemifloxacin 320mg once daily for 5 days with an approved antibacterial comparator given for 7 days. The inclusion criteria targeted an ABECB study population that represented patients who would benefit from antibacterial therapy but were appropriate for oral therapy.

Clinical response, based on the resolution of signs and symptoms of ABECB in the Clinical Per Protocol Population (CPP) at follow-up (FU), served as the primary efficacy parameter in the principal clinical studies. Secondary endpoints included bacteriological and clinical responses in the patients with an identified pathogen (the Bacteriology intent to treat (BITT) and Bacteriology Per Protocol Population (BPP)). None of the studies were designed to test non-inferiority for secondary endpoints. The following table summarizes the key design elements and the outcomes for the principal studies in ABECB.

Table 1. Efficacy Results for Gemifloxacin in ABECB: Principal Studies

	Study 068		***Study 070***		***Study 212***	
DESIGN:	*randomized, double-blind, double-dummy, multicenter, parallel group*		Same as 068		*Same as 068*	
Gemifloxacin regimen	*320 mg qd x 5 days*		*Same as 068*		*Same as 068*	
Comparators	*Clarithromycin 500 mg bid x 7 days*		*Amoxicillin/clavulanate 500/125 mg tid daily x 7 days*		*Levofloxacin 500 mg qd x 7 days*	
Countries	*Europe, USA and Canada*		*Europe*		*Europe and USA*	
Primary Efficacy Analysis	*Clinical response in the clinical per protocol population at follow-up (PP FU)*		*Same as 068*		*Same as 068*	
Prootocol-specified non-inferiority limit	*-10*		*-10*		*-13*	
Number of centers	*93*		*112*		*62*	
Number of patients randomized to gemifloxacin	*340*		*304*		*182*	
OUTCOME						
	Gemifloxacin 320mg qd 5 days	*Clarithromycin 500mg bid 7 days*	*Gemifloxacin 320mg qd 5 days*	*Augmentin 500/125mg tid 7 days*	*Gemifloxacin 320mg qd 5 days*	*Levofloxacin 500mg od 7 days*
Clinical response CPP FU	*86.0%*	*84.8%*	*93.6%*	*93.2%*	*88.2%*	*85.1%*
Difference (95% CI)	*1.2 (-4.7, 7.0)*		*0.3 (-3.9, 4.6)*		*3.0 (-4.7, 10.7)*	
Bacteriological response PP FU	*85.0%*	*72.7%*	*90.9%*	*79.5%*	*78.4%*	*85.7%*
Difference (95% CI)	*12.3 (-4.9, 29.5)*		*11.4 (-3.3, 26.0)*		*-7.3 (-23.8, 9.2)*	

Demographic characteristics were equally balanced between treatment arms for all studies. The study population generally consisted of middle aged, white, long-term smokers, with a mean 12-year history of ABECB and 1-4 exacerbations of ABECB in the past year. Males and females were equally represented in the principal studies. About a third of patients in Studies 070 and 212 had a FEV1<50% of predicted. Patients with severe ABECB (stage 3) were a minority.

The per pathogen bacteriologic outcomes in the bacteriological per protocol population are summarized in *Table 2.*

Table 2. Per Pathogen Bacteriologic Response in the Pivotal ABECB Studies*(excludes recurrences)

Pathogen	*Gemifloxacin*		*Comparator*	
Hemophilus influenzae	*n/N*	*%*	*n*	*%*
068	*11/12*	*91.7*	*6/6*	*100*
070	*14/14*	*100*	*14/15*	*93.3*
212	*7/7*	*100*	*10/11*	*90.9*
TOTAL	***32/33***	***97.0***	***30/32***	***93.7***
Streptococcus pneumoniae				
068	*6/7*	*85.7*	*5/5*	*100*
070	*6/6*	*100*	*8/8*	*100*
212	*4/4*	*100*	*4/5*	*80*
TOTAL	***16/17***	***94.1***	***17/18***	***94.4***
Moraxella catarrhalis				
068	*5/5*	*100*	*5/5*	*100*
070	*13/14*	*92.8*	*12/12*	*100*
212	*5/6*	*83.3*	*14/14*	*100*
TOTAL	***23/25***	***92.0***	***31/31***	***100***
Hemophilus parainfluenzae				
068	*6/6*	*100*	*5/5*	*100*
070	*2/2*	*100*	*0*	*0*
212	*7/7*	*100*	*5/6*	*83.3*
TOTAL	***15/15***	***100***	***10/11***	***90.9***
Staphylococcus aureus				
068	*4/4*	*100*	*5/6*	*83.4*
070	*1/1*	*100*	*7/7*	*100*
212	*4/4*	*100*	*4/5*	80
TOTAL	***9/9***	***100***	***16/18***	***88.9***

In the analyses in this table successful response refers to proven and presumed eradication only.

Acute Exacerbation of Chronic Bronchitis: Supportive Studies

Two clinical trials, Study 069 and 207, provided additional supportive evidence of the efficacy and safety of gemifloxacin 320 mg po qd for 5days in the treatment of ABECB. Study 069 was of identical design as the principal studies, however, the dose of the comparator, Trovan (trovafloxacin), utilized in Study 069 was based on the approved dose in Europe (200mg qd for 5 days) whereas the approved dose in the United States is 100mg qd for 7-10 days. Hence, Study 069 was considered as a supportive rather than a principle study. The population of patients recruited into Study 069 was was very similar to the patient populations in the principal clinical studies in ABECB in terms of baseline characteristics and severity of ABECB.

Study 207 was designed to investigate the safety and efficacy of gemifloxacin in hospitalized patients with ABECB and the impact of oral versus parenteral therapy on time to discharge and cost. Compared to the study population in the pivotal trials,

patients in Study 207 were slightly older and had more frequent exacerbations of ABECB in the last 12 months. Many required oxygen and were treated with systemic corticosteroids, indicators that the patients may have been considered to have more severe ABECB. However, these indicators have not been shown to correlate with the need for parenteral antimicrobial therapy. This study was not blinded (open-label) and patients in Study 207 were recruited from centers in Europe, Mexico and South Africa, and did not include patients in the United States.

Table 3. Selected Demographic and Baseline Characteristics in the Supportive ABECB Studies

	Study 068		Study 070		Study 212		Study 069		Study 207	
	Gemi N=340	Clari N=351	Gemi N=304	Amox/Clav N=296	Gemi N=182	Levo N=179	Gemi N=302	Trova N=314	Gemi N=138	Ceftr IV /Cefurox po N=136
Age										
Mean Age (SD)	58.8 (12.0)	58.6 (11.9)	64.2 (11.7)	63.9 (12.1)	61.6 (11.6)	63.4 (10.5)	60.8 (11.0)	62.4 (11.2)	68.1 (9.8)	67.1 (10.3)
Exacerbations (past 12 months)										
0	65 (19)	66 (18.8)	19 (6.3)	24 (8.1)	25 (13.7)	20 (11.2)	31 (10.3)	36 (11.5)	0	0
1-4	236 (69.4)	245 (69.8)	226 (74.3)	231 (78.0)	143	136 (76.0)	230 (76.2)	240 (76.4)	98 (71.0)	90 (66.2)
>4	36 (10.6)	40 (11.4)	58 (19.1)	41 (13.9)	14 (7.7)	23 (12.8)	38 (12.6)	37 (11.8)	40 (29.0)	46 (33.8)
Use of Supplemental Oxygen, n (%)										
Yes	32 (9.4)	23 (6.6)	14 (4.6)	9 (3.0)	18 (9.9)	19 (10.7)	8 (2.6)	12 (3.8)	34 (24.6)	33 (24.3)
Use of Systemic Steroids in last year, n (%)										
Yes	72 (21.2)	75 (21.4)	76 (25.0)	72 (24.3)	50 (27.5)	52 (29.2)	73 (24.2)	96 (30.6)	65 (47.1)	61 (44.9)
Current Smoker*, n(%)	*smoked regulary in last month		*smoked regularly in last month		*Currently smoke		*Smoked regulary in last month		*Current smoker	
Yes	146 (42.9)	161 (45.9)	130 (33.9)	117 (39.5)	81 (44.5)	67 (37.5)	114 (37.7)	117 (37.3)	27 (19.6)	30 (22.1)
Number of Pack Years patients has smoked n (%)										
0	72 (21.2)	80 (22.8)	96 (31.6)	96 (32.4)	38 (20.9)	39 (21.9)	99 (32.8)	83 (26.4)	28 (20.3)	30 (22.1)
>0-30	123 (36.2)	123 (35.0)	112 (36.8)	113 (38.2)	62 (34.1)	43 (24.2)	120 (39.7)	142 (45.2)	61 (44.2)	58 (42.6)
>30	143 (42.1)	147 (41.9)	92 (30.3)	82 (27.7)	82 (45.1)	96 (53.9)	83 (27.5)	89 (28.3)	49 (35.5)	48 (35.3)

In Study 069 the response rate in the Clinical Per Protocol Population (CPP) at follow-up (FU) was 91.5% for gemifloxacin and 87.6% for comparator (Table 4). The clinical response rate in the CPP at FU in Study 069 were similar to those observed in the principal clinical studies. In Study 207 the clinical response rate in the CPP at FU was 86.8% for gemifloxacin and 81.3% in comparator. The respone rates in Study 207, which enrolled hospitalized patients were lower than the success rates observed for the principal studies.

Table 4. Clinical and Bacteriological Response at Follow-Up in the Supportive ABECB Studies

	Success Rate		
	Gemifloxacin	*Comparator*	*Treatment Difference*
	% (n/N)	*% (n/N)*	*% (95% CI)*
Clinical Response in the Clinical PP Population			
069	*91.5 (249/272)*	*87.6 (241/275*	*3.9 (-1.2,9.0)*
207	*86.8 (105/121)*	*81.3 (91/112)*	*5.5 (-3.9,14.9)*
Clinical Response in the Clinical ITT Population			
069	*89.4 (270/302)*	*83.1 (261/314)*	*6.3 (0.9, 11.7)*
207	*82.6 (114/138)*	*72.1 (98/136)*	*10.5 (0.7, 20.4)*
Response in the Bacteriology PP Population			
069 Bacteriological	*86.8 (46/53)*	*82.4 (42/51)*	*4.4 (-9.4,18.3)*
207 Clinical	*80.9 (38/47)*	*87.0 (40/46)*	*-6.1 (-21.0, 8.8)*
Bacteriological	*63.8 (30/47)*	*68.3 (28/41)*	*-4.5 (-24.3, 15.3).*
Response in the Bacteriology ITT Population			
069 Bacteriological	*83.6 (46/55)*	*74.1 (43/58)*	*9.5 (-5.4, 24.4)*
207 Clinical	*81.3 (39/48)*	*82.4 (42/51)*	*-1.1 (-16.3, 14.1)*
Bacteriological	*62.5 (30/48)*	*60.8 (31/51)*	*1.7 (-17.4, 20.9)*

Additional Studies in ABECB Evaluating Other Outcomes

The Applicant conducted additional studies of gemifloxacin in ABECB to evaluate several other outcomes beyond safety and efficacy. These additional outcomes include the following:

- Exacerbation-free intervals (Study 112, 105, 139)
- Time to discharge in patients requiring hospitalization (Study 207)
- Number of hospitalizations due to RTI-related episodes (Study 139)
- Time to eradication of bacterial pathogens (especially H. influenzae) (Study 105 & 068)

These additional studies performed from which the data were derived to investigate these additional outcomes are as follows:

- Study 105 - small PK/PD study (n=163) conducted in patients at risk for recurrence
- Study 112 - a large multinational study (n=1805) evaluating time to next exacerbation out to 4 months post therapy
- Study 139 - a longer term follow-up study added on to Study 068 (n=438). In Study 139 patients were followed for 26 weeks to evaluate time to next exacerbation.

In addition to data from these three studies (Studies 105, 112, and 139), data from the Study 068 and Study 207 were also used to provide information in support of these additional outcomes.

Study 105

Study 105 was designed to investigate the pharmacokinetic and pharmacodynamic properties of gemifloxacin versus clarithromycin in patients with ABECB at risk of early recurrence. The study also attempted to characterize the cytokine response, the role of nasopharyngeal (NP) colonization in ABECB recurrences, the change in quality of life as measured by the St George Respiratory Questionnaire (SGRQ), and other indicators of clinical and bacteriologic response. There were no primary efficacy parameters for this exploratory study. The protocol stated that no formal statistical testing will be carried out, and results will be for descriptive purposes only. The Applicant did not provide any adjustment for the type one error rate. The following 10 efficacy parameters were listed in the protocol:

- Clinical response at end of therapy and at follow-up
- Bacteriological response at end of therapy and at follow-up
- Time to bacterial eradication over all pathogens and by pathogens
- Change in clinical signs and symptoms
- Change in response to the SGRQ from screening
- Change in percent predicted FEV1
- Change in inflammatory parameters
- Proportion of patients with eradication of NP colonizing organisms *(S. pneumoniae, S. aureus, M. catarrhalis,* and *H. influenzae*) on Day 1, Day 4, end of therapy and follow-up
- Time from the follow-up visit to next episode of ABECB
- Change in sputum cytology

Given that there are approximately 31 comparisons accounting for the different pathogens and time points for analysis, there would be a very high probability of seeing a statistically significant result by chance alone.

Study 112

Study 112 was a randomized, double-blind, double-dummy, multicenter study conducted in 10 countries. The objective of the study was to establish superiority of gemifloxacin 320 mg once daily for 5 days over clarithromycin 500 mg bid for 7 days in time to next exacerbation of chronic bronchitis. Secondary efficacy parameters included clinical response at Visit 2 and Visit 3 (Visit 3 was scheduled 16-18 weeks after Visit 2) and time to resolution of initial episode of ABECB. This study also collected a number of pharmacoeconomic and health related quality of life measures.

Study 139

Study 139 was a double-blind, observational parallel/ follow-on study to study 068 to assess the proportion of patients who had resolved from their initial episode and remained recurrence free for ABECB. Following the first 4 to 5 weeks of study 068 in the USA and Canada, patients were recruited to attend two further visits, at Weeks 12 and 26 (following the screening visit for study 068). Patients would be assessed for recurrence of ABECB at Visit 2 (day 28-35), Visit 3 (week 12) and Visit 4 (week 26). Investigators telephoned patients between visits at Week 8, Week 17 and Week 21 to check on the patient's status. The primary analysis compared the proportion of patients who had not yet had a recurrence of ABECB across treatments at each visit and call. This approach results in a total of 6 analyses. No adjustment for the type 1 error rate was made. Secondary parameters included the number of recurrences, quality of life measures, use of resources measures, and indirect cost measures.

Prolonged exacerbation-free intervals (Study 112, 105, 139)

Three studies measured the time to recurrence of ABECB. The results from these studies regarding this outcome were as follows. Study 139 concludes that gemifloxacin provides an advantage in the proportion of recurrence free patients (primary endpoint), whereas Study 112 finds no such advantage in time to next exacerbation (primary efficacy endpoint). Study 105 evaluated time to recurrence as one of 12 efficacy parameters. Study 105 found that therapy with gemifloxacin resulted in more patients with recurrences as well as an earlier time to recurrence.

For study 139, the Applicant states that the proportion of patients who were recurrence free was statistically higher for gemifloxacin with a difference in point estimates of 12%. However, this endpoint was not statistically significant using a Bonferroni adjustment (limit = 0.008 = 0.05/6). The results of this analysis are provided in *Table 5.*

Table 5. Proportion of patients resolved and with no recurrence Study 139

Visit/Call	Gemifloxacin	Clarithromycin	P-value
Visit 2 (week 4-5)	176/202 (87.1)	173/214 (80.8)	0.081
Call 1 (week 8)	165/195 (84.6)	159/197 (80.7)	0.039
Visit 3 (week 12)	148/183 (80.9)	131/176 (74.4)	0.143
Call 2 (week 17)	135/179 (75.4)	118/176 (67.0)	0.084
Call 3 (week 21)	117/160 (73.1)	97/156 (62.2)	0.110
Visit 4 (week 26)	120/169 (71.0)	100/171 (58.5)	0.016

Study 112 did not find any difference in recurrence rates between gemifloxacin and clarithromycin in time to next exacerbation. The risk for recurrence was not significantly different between treatment groups (hazard ratio 0.98, 95% CI 0.84, 1.15) as can be seen in the following Kaplan Meier plot (*Figure 1*).

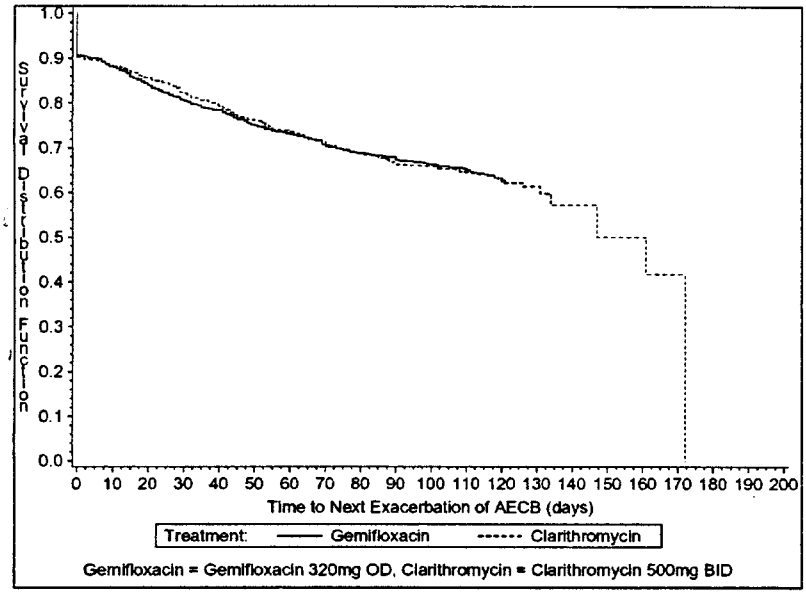

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Figure 1. Kaplan – Meier Plot: Time to Next Exacerbation of Chronic Bronchitis (ITT Population) – (Source: Applicant's Figure 2 from Study Report for Study 112)

The following table gives the results of the proportion of patients remaining recurrence free. There was not a statistically significant different between the two arms.

Table 6. Proportion of patients remaining recurrence free Study 112

ITT analysis	Gemifloxacin	Clarithromycin	P-value
By 17-20 weeks after end of therapy	595/903 (65.9)	586/896 (64.5)	0.827

As stated above, study 105 also looked at time to recurrence as one of its many endpoints. Recurrence rate of ABECB was higher for gemifloxacin (60%, 50/83) than for clarithromycin (53%, 42/80) and occurred earlier in the gemifloxacin treatment group (median time to recurrence 22 vs. 46 days for gemifloxacin and clarithromycin, respectively). The following table gives the proportion of patients for whom ABECB resolved and who remain recurrence-free.

Table 7. Proportion of patients resolved and with no recurrence - Study 105

ITT population	Gemifloxacin	Clarithromycin	P-value
Week 11 (approx.)*	33/83 (39.8)	38/80 (47.5)	0.319

Source: Data from Table 43 of sponsor's study report. page 121/1646
*Patients were seen at follow-up on Day 21-25 and at four post-follow-up visits (every 2 weeks after the follow-up visit). Patients who withdrew before an exacerbation were censored.

The Kaplan Meier plots for time to next episode of ABECB for the ITT population both including (*Figure 2*) and excluding (*Figure 3*) (respectively) patients who had a time to next episode of 0 days from Study 105.

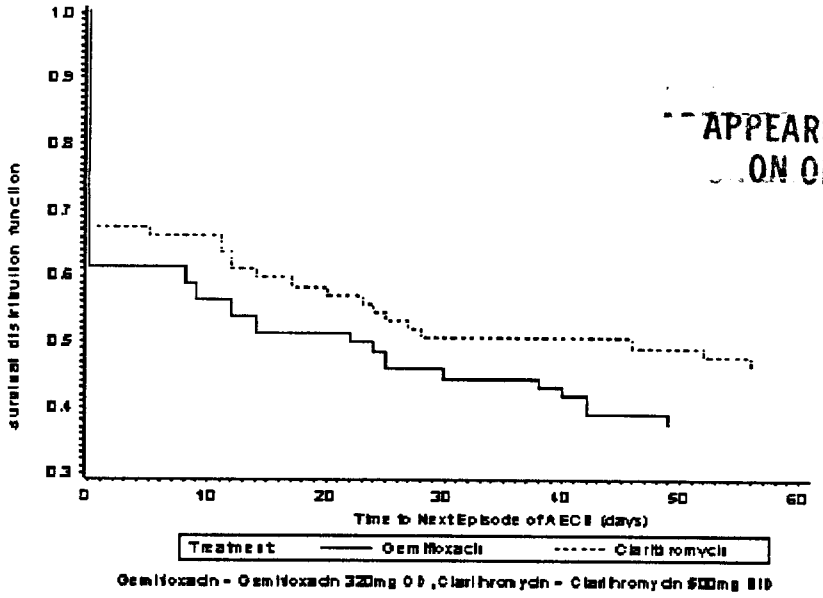

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Figure 2. Time to Next Episode of ABECB – Kaplan Meier Plot (ITT Population) – Source: Applicant's figure 3 from the Study Report for Study 105

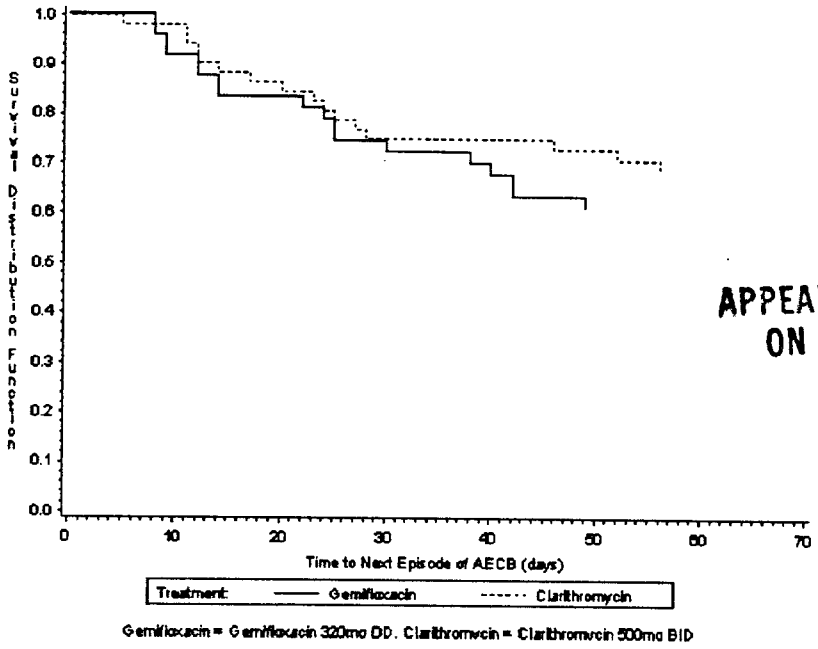

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Figure 3. Time to Next Episode of ABECB – Kaplan Meier Plot – Clinical Success (Intent to Treat) Applicant's figure 3 from the Study Report for Study 105

In summary, of the 3 studies that measured the endpoint time to next episode of ABECB, one study favored gemifloxacin, one study favored clarithromycin, and one study showed no difference.

Time to discharge in patients requiring hospitalization (Study 207)

In Study 207, a supportive open-label study, the sponsor also evaluated the duration of hospitalization in inpatients with ABECB along with its primary endpoint of clinical response at follow-up. This endpoint was one of four secondary endpoints with no adjustment for multiple comparisons proposed. This study compared gemifloxacin 320mg for 5 days with parenteral ceftriaxone followed by oral cefuroxime axetil in the treatment of hospitalized adult patients. The Applicant's analysis shows that patients who received gemifloxacin had a median time to discharge that was 2 days shorter than that of the comparator. The Applicant determined that there was a statistically significant difference in time to discharge based on a Wilcoxon p-value of 0.04. However, the hazard ratio of 0.83 is not statistically significantly different from one (0.83, 95% C.I. 0.64, 1.07) and the log-rank p-value is 0.16. The difference in means between the two groups is 0.5 days (11.1 vs. 10.6). The Kaplan Meier plot of this data is provided in *Figure 4.*

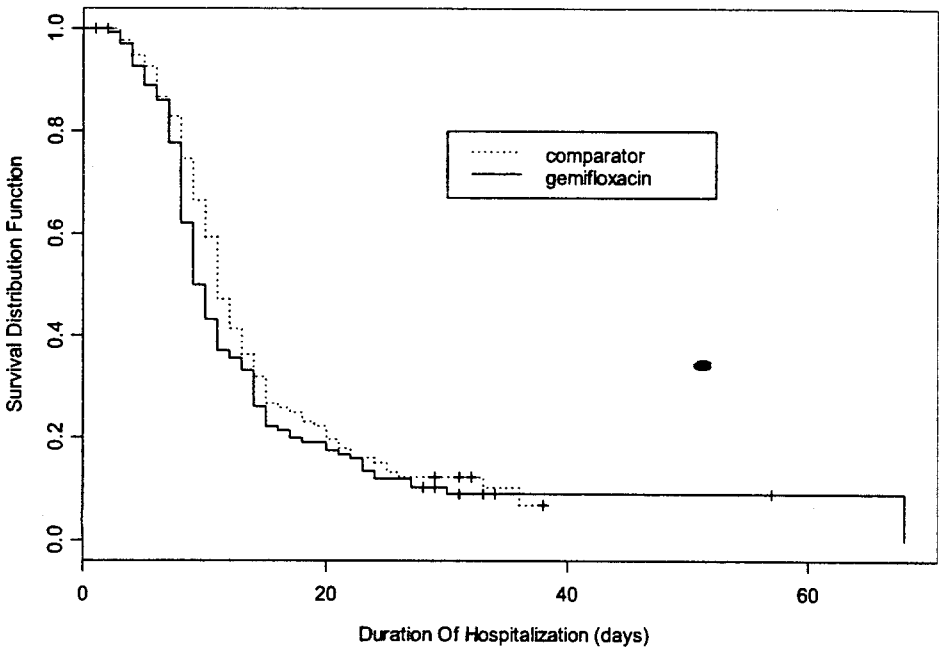

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Figure 4. Time to Discharge – Kaplan Meier Plot Intent-To-Treat Population – (Source: Applicant's Study Report for Study 207 Figure 13.01)

Note that patients in the IV group received at least one dose of intravenous medication and that preparation for intravenous administration of therapy alone could explain the difference in the mean time to discharge. Furthermore, resolution of symptoms, resource utilization, quality of life and readmissions did not differ between study arms.

As part of a pharmacoeconomics analysis, the sponsor also conducted an analysis of duration of hospitalization using a general linear model. Treatment was not a statistically significant variable in the model ($p = 0.55$).

Hospitalizations due to respiratory tract infection (RTI) - related episodes (Study 139)

The number of patients hospitalized for an RTI-related episode over the 26-week study period was one of many secondary endpoints under the category of use of resources in Study 139. The number of patients with an RTI-related hospital episode by Visit number is provided in *Table 8.* Note that there was not a significant difference between treatment groups in the number of patients with an RTI-related hospital episode.

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Table 8. Study 139 Number of Patients with an RTI-related Hospital Episode at Each Visit

Visit	Gemifloxacin N=214 n/N (%)	Clarithromycin N=224 n/N (%)	Difference (95% CI)	P-value
Visit 2	1/202 (0.5)	5/214 (2.3)	-1.8 (-4.1. 0.4)	0.217
Visit 3	2/183 (1.1)	4/176 (2.3)	-1.2 (-3.9, 1.5)	0.441
Visit 4	3/169 (1.8)	5/179 (2.9)	-1.1 (-4.4, 2.1)	0.723
Total	5/214 (2.3)	14/224 (6.3)	-3.91 (-7.67,-0.15)	0.059

Source: NDA 21-158, Study Report for Study 139, Tables 28 and 29

Additional secondary "resource utilization" endpoints included length of RTI-related hospital stay, number of days on antibiotic therapy, number of days on RTI-related antibiotic therapy, and number of RTI-related physician visits. None of these endpoints showed a difference between treatments.

Time to eradication of bacterial pathogens - (especially* H. influenzae*) - (Study 105 and 068)

The time to bacterial eradication of *H. influenzae* was evaluated in two clinical studies – Study 105 and Study 068. The results from each of these two studies are summarized in the sections that follow.

Study 105

In Study 105 the Applicant found that bacterial pathogens were more rapidly eradicated in patients treated with gemifloxacin compared to those treated with clarithromycin. By day 6, only 2% (1/66) of gemifloxacin treated patients had persistently positive sputum cultures, compared to 28% 16/58 in the clarithromycin group. The median time to bacteriological eradication of all pathogens was 1 day for gemifloxacin and 2.5 days for clarithromycin. Results from this study for *H. influenzae* showed that on Day 1 the bacterial eradication rates of *H. influenzae* on gemifloxacin was 18/23 (78%) compared to 13/31 (42%) for clarithromycin. The median time to eradication of *H. influenzae* was 1 day for gemifloxacin and 2 days for clarithromycin. Again, this was based on one of many efficacy parameters analyzed in this study for descriptive purposes.

The following two tables show the number of patients with continued clinical success at the six time points for this study for both the subset of patients with any pathogen (*Table 9*) and the subset of patients with *H. influenzae* (*Table 10*). When taking this finding into consideration within the context of the clinical and bacteriological outcomes in the principal clinical studies which demonstrated non-inferiority of gemifloxacin to its comparators its not clear that the time to bacterial eradication has an impact on ultimate patient outcomes in ABECB.

Table 9. Sustained Clinical Success in Patients with Baseline Pathogens -Study 105

Clinical Success (ITT) n (%)	***Gemifloxacin N=66***	***Clarithromycin N=58***
EOT	*55 (83.3%)*	*45 (77.6%)*
Follow-up	*38 (57.6%)*	*39 (67.2%)*
Visit 1	*30 (45.5%)*	*33 (56.9%)*
Visit 2	*25 (37.9%)*	*27 (46.6%)*
Visit 3	*20 (30.3%)*	*27 (46.6%)*
Visit 4	*19 (28.8%)*	*24 (41.4%)*

Table 10. Sustained Clinical Success in Patients with *H. influenzae* - Study 105

Clinical Success (ITT) n (%)	***Gemifloxacin N=23***	***Clarithromycin N=31***
EOT	*19 (82.6%)*	*24 (77.4%)*
Follow-up	*16 (69.6%)*	*21 (67.7%)*
Visit 1	*12 (52.2%)*	*18 (58.1%)*
Visit 2	*8 (34.8%)*	*14 (45.2%)*
Visit 3	*7 (30.4%)*	*14 (45.2%)*
Visit 4	*6 (26.1%)*	*13 (41.9%)*

Study 068

Study 068, one of the principal studies, also contained a sub-study to evaluate the time to *H. influenzae* eradication, which was one of the 6 listed secondary analyses. This analysis was restricted to the subgroup of patients enrolled in the sub-study who had *H. influenzae* cultured at baseline (n=24). These patients had their bacteriological outcome determined daily from days 1 to 6. An outcome of eradication, persistence, or unable to be determined was given at each time point. Time to bacterial eradication was defined as the time in days to the first outcome of bacterial eradication. Kaplan Meier plots of time to eradication were presented along with the two pre-specified analyses of time to eradication and an analysis of proportion of patients with eradication on Day 1.

The number and percent of *H. influenzae* eradicated by treatment group at Days 1 through Day 3 are summarized in Table 11. The proportion of patients with bacteria eradicated at Day 1 was not statistically significantly different between the two treatment arms. However, the difference in time to bacterial eradication was statistically significant (p=0.02 based on a log-rank test).

Table 11. Number and Percent of *H. influenzae* Eradicated by Study Day - Study 068 Sub-study

	Treatment Group	
	Gemifloxacin 320 mg po qd x 5 days N = 12	***Clarithromycin 500 mg po bid x 7 days N = 12***
Day 1	*7 (58%)*	*3 (25%)*
Day 2	*11(92%)*	*7 (58%)*
Day 3	*11 (92%)*	*8 (67%)*
	1 subject was censored on day 0	*1 subject was censored on day 0* *1 subject was censored on day 3* *2 subjects were censored on day 4*

The Kaplan-Meier plot for the time to eradication of *H. influenzae* by treatment group is provided in Figure 5.

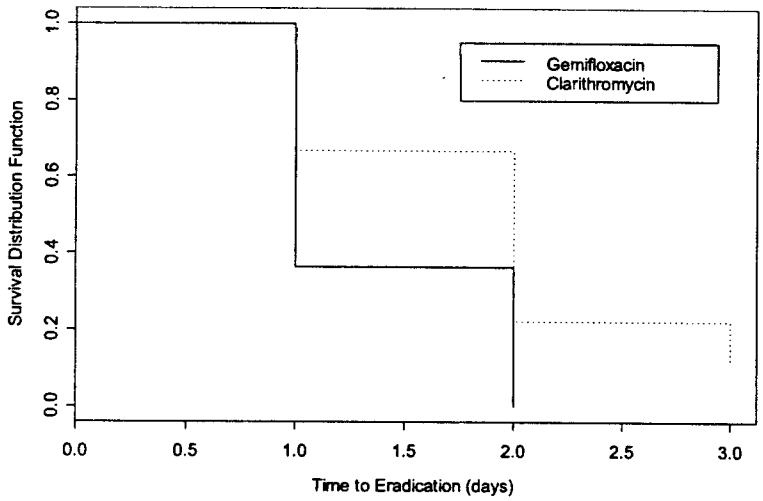

Figure 5. Time to Eradication for *H. influenzae* – Kaplan-Meier Plot – Bacterial Eradication Analysis Population: Source- Study Report for Study 068, Figure 13.01

As noted previously in the discussion of the results of Study 105 the clinical and bacteriological outcomes in the principal clinical studies demonstrated non-inferiority of gemifloxacin to its comparators; it is not clear that the time to bacterial eradication has an impact on ultimate patient outcomes in ABECB. In Study 068, the clinical cure rates for gemifloxacin were less than or equal to clarithromycin at the time points evaluated with the exception of the per protocol analysis at follow-up (*Table 12*).

Table 12. Clinical Cure in Patients with *H. influenzae* - Study 068 sub-study

Clinical Cure	***Gemifloxacin***	***Clarithromycin***
PP at EOT	*8/10 (80%)*	*10/12 (83%)*
PP at follow-up	*8/10 (80%)*	*8/12 (67%)*
ITT at EOT	*8/12 (67%)*	*10/12 (83%)*
ITT at follow-up	*8/12 (67%)*	*8/12 (67%)*
ITT at long-term follow-up	*6/12 (50%)*	*7/12 (58%)*

The sponsor showed in two studies (Studies 105 and 068 (sub-study) that eradication of *H. influenzae* in the sputum occurs sooner for gemifloxacin than for clarithromycin. Though, these results were based on analyses that were not adjusted for multiple comparisons, they are consistent across the two studies. However, this earlier eradication of *H. influenzae* has not been shown to translate into a clinical benefit.

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Edward Cox
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